New Diagnostic Techniques For Functional Lower Urinary Tract Disorders

Fawzy Farag

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New Diagnostic Techniques for Functional Lower Urinary Tract Disorders

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INTRODUCTION

Lower Urinary Tract Symptoms (LUTS) are divided into storage phase symptoms, voiding phase symptoms and post micturition symptoms. Overactive bladder (OAB) syndrome is one of the storage phase disorders that presents with urgency with or without urgency incontinence, usually with frequency and nocturia in absence of infection or any other obvious pathology[1]. OAB syndrome is highly prevalent in Western society, 13% of women and 11% of men above 18 years have these symptoms.

Clinical assessment of patients with OAB symptoms can be summarized as follows[2]:

1. History and clinical examination: to exclude underlying medical disease such as upper motor neuron lesion, diabetes mellitus or diabetes insipidus. Urological diseases can be the cause of OAB symptoms and therefore it is necessary to exclude urinary tract infection, reduced bladder capacity, interstitial cystitis, vesical tumors or stones and urethral syndrome. Some gynecological conditions can also resemble cause OAB symptoms such as, stress urinary incontinence, pelvic organ prolapse, fibroids and postmenopausal genital atrophy.
2. Voiding diary and urgency severity scales to measure the severity of urgency severity e.g. Urgency Severity Scales, Patient Perception of Intensity of Urgency Score and Urgency Perception Score.

3. Quality of Life questionnaires.
4. Urine analysis, culture and sensitivity in all cases of incontinence to exclude UTI.
5. Refractory and/or complex symptoms may receive one or all of the following tests:

   a) Uroflowmetry to exclude a significant post void residual urine

   b) Cystourethroscopy in patients with hematuria, painful bladder syndrome and recurrent incontinence; it is of great value to exclude vesical tumor or stones.

   c) Filling cystometry to prove the presence of detrusor overactivity (DO), which is a urodynamic finding in about 60% of women with OAB[3].

Voiding LUTS can be caused by bladder outlet obstruction (BOO). Assessment of patients with voiding LUTS includes[4]:

1. A focused history taking supported by voiding diaries and International Prostate Symptoms Score (IPSS) questionnaire.
2. Urinary flowmetry can prove the presence of diminished flow rate and high residual urine suggestive of BOO, but can still indicate a case of bladder hypo-contractility, which makes its specificity questionable.
3. Cystoscopy can confirm the presence of an organic cause of BOO, such as enlarged prostatic gland or stricture urethra, but still lack a functional or dynamic assessment of voiding act.
4. Pressure flow studies can confirm the presence of high voiding pressure versus low flow rate, and can also exclude the presence of detrusor hypo-contractility. They can be saved for patients who might necessitate surgical interference to treat LUTS.

Filling cystometry and pressure flow studies are invasive procedures as they imply insertion of a gas- or water-filled urethral catheter in the bladder through which water is infused at room temperature with certain filling rates as requested by the primary patient's physician. This catheter is provided with a pressure sensor to monitor changes in intravesical pressure (P_{ves}) during filling; another catheter is to be inserted in the rectum to monitor abdominal pressure (P_{abd}) changes. Detrusor pressure (P_{det}) changes can be obtained by subtracting the P_{abd} from the P_{ves} values[1,5].

The invasive nature of filling cystometry can lead to various morbidities, such as patient's discomfort, pain and sometimes urinary tract infections (UTI)[6]. Therefore, it is worthwhile to develop non-invasive techniques that can replace the conventional urodynamics in the diagnosis of functional lower urinary tract disorders.

The knowledge about non-invasive urodynamics is growing and gaining reasonable evidence, at least on theoretical and scientific basis. Some trials were done to develop less- or non-invasive diagnostic tools to replace conventional urodynamics, for example ultrasonographic measurement of bladder wall thickness (BWT)[7,8], detrusor wall thickness (DWT)9,10], ultrasonographic estimated bladder weight (UEBW)[11] and measurement of isovolumetric bladder pressure[12]. Nerve Growth Factor (NGF) and other neurotrophins as biomarkers for DO were also investigated[13].

This thesis describes three new non-invasive diagnostic techniques for functional lower urinary tract disorders.

Near-infrared spectroscopy (NIRS) is an imaging technology. NIRS of biologic tissues enables non-invasive evaluation of oxygen dependent hemodynamic changes in these tissues by measurement of the relevant changes in the concentration of tissue hemoglobin. Oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (HHb) respectively represent the oxygen supply and consumption of the tissue. The sum of O_2Hb and HHb is Hb_{sum}, it represents the total blood perfusion of the tissue under monitoring[14-16].

In *chapters 1 and 4*, systematic reviews are presented of the clinical studies that have been done to develop non-invasive diagnostic tools in the storage and voiding phases of the micturition cycle.

In *chapters 2 and 3*, a novel diagnostic technique for DO in patients with OAB syndrome that has been developed at the Department of Urology of the Radboud University Nijmegen Medical Centre, The Netherlands. In these two chapters, the feasibility, reproducibility and accuracy of NIRS in the diagnosis of DO were determined in patients with OAB symptoms.

Chapter 5 describes our experience with a new home-based uroflowmeter in the diagnosis of voiding LUTS. *Chapter 6* describes the results of NIRS monitoring of the bladder activity during voiding in men with LUTS. The preliminary observations from our trial to apply 2D ultrasonography in real-time monitoring of voiding activity in men with LUTS are presented in *chapter 7*. A summary of all these studies with future directions is given in *chapter 8*.

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CHAPTER 1

Non-Invasive Techniques in the Diagnosis of Bladder Storage Disorders

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Abstract

Aims

To review the clinical studies, which have been performed to develop non-invasive diagnostic tools in the storage phase of the micturition cycle.

Methods

Pub Med and Web of Science searches were carried out. The search covered the published data of non-invasive diagnostic techniques for detrusor overactivity (DO) and/or low compliance bladder in patients with urinary storage symptoms. The pathophysiological and clinical relevance of these methods were addressed. Diagnostic accuracy of these techniques was scrutinized.

Results

18 studies were included in the review. Ultrasonography and biomarkers were the most investigated techniques in the diagnosis of storage disorders. Assessment of diagnostic accuracy was possible in four studies. The heterogeneity in data reporting was too high to conduct a meta-analysis. Ultrasonographic parameters and cut-off values have been developed to define DO, such as bladder wall thickness (BWT), detrusor wall thickness and bladder weight. The likelihood ratio of vaginal ultrasonography in the measurement of BWT was good. Guidelines are currently developed to standardize the methodologies applied in these techniques. Laboratory biomarkers of DO are recently gaining more attention, but their specificity for DO should be carefully defined. Near-infrared spectroscopy (NIRS) is a potential non-invasive diagnostic method that is able to detect the DO episodes in real-time. However, a solution needs to be found for motion artifacts in this technique.

Conclusions

Non-invasive diagnostic techniques for storage disorders show limited progress with some limitations. These techniques still cannot replace the standard filling cystometry in routine clinical practice yet.

Non-Invasive Techniques in the Diagnosis of Bladder Storage Disorders

Introduction

Overactive bladder (OAB) syndrome is highly prevalent in the Western community where 13% of women and 11% of men above 18 years have OAB symptoms[1]. It negatively affects the patient's quality of life[2]. OAB syndrome is defined as 'urgency', with or without urgency incontinence, usually with frequency and nocturia in absence of infection or other obvious pathology[3]. Detrusor overactivity (DO) is a major cause of these symptoms. Although a diagnosis of OAB syndrome would be derived from these symptoms, some other bladder disorders may share these non-specific symptoms. This fact makes it reasonable to clarify the actual etiology and pathophysiology of OAB syndrome applying the available diagnostic techniques[4].

Filling cystometry is the current standard urodynamic test applied in the diagnosis of DO in patients with OAB syndrome. Clarke[5] believed that it is inappropriate to rely on the symptoms of the lower urinary tract alone in the diagnosis and planning treatment strategies. He found that the symptoms of urinary stress incontinence, although associated with urodynamic stress incontinence in 95% of cases, were also associated with DO in 64% of cases. This ratio would have been missed if the diagnosis was based on symptoms only. Salvatore *et al.*[6] reported a significant difference in tolterodine efficacy when used in different forms of DO. The authors assumed a substantial correlation between the pathophysiology of DO either spontaneous 'myogenic' or provocative 'neurogenic'. This shows the importance of addressing the definite etiology and pathology of OAB syndrome, especially in planning treatment strategies.

Urodynamics equipment measures pressure changes in the bladder suggestive of DO or poor compliance. In order to monitor these pressure changes, insertion of transurethral and rectal catheters is mandatory[7]. This can explain the invasive nature and potential morbidity of filling cystometry[8]. Moreover, authors agree that the correspondence between OAB symptoms and DO is not that perfect[9]; one study showed that only 55% of women with OAB were diagnosed urodynamically to have DO, while only 30% of women with a urodynamic diagnosis of DO had these symptoms[10]. Radley *et al.*[11] found that conventional cystometry classified only 32 out of 106 women with OAB symptoms as having DO, while ambulatory urodynamics classified 70 women as having DO.

The above-mentioned drawbacks make it worthwhile to develop new non-invasive diagnostic tools that can replace the conventional cystometry in the diagnosis of bladder storage disorders. This is important in certain patient groups that need to undergo regular urodynamic evaluation.

Methods

Pub Med and Web of Science searches (1980–2010) were carried out to obtain the literature. Keywords used in search were: urinary bladder, overactive; low compliance bladder; diagnosis; non-invasive; ultrasonography; laboratory techniques and procedures; biological markers; spectroscopy, near-infrared; nerve growth factor; bladder weight; bladder wall thickness; detrusor wall thickness. The search was limited to studies conducted in humans and written in English. The target disease was DO or low compliance bladder in adult subjects with bladder storage symptoms. An article to be included had to describe a non-invasive diagnostic test being evaluated as compared to a reference urodynamics test of bladder storage disorders. Articles evaluating treatment and/or surgery outcomes were not included. For every technique, the index study was presented followed by the more recent studies.

We focused on the rational implied to address the pathophysiological and clinical relevance of the non-urodynamic parameters derived from these studies. Studies providing diagnostic cut-offs were assessed for their quality applying the QUADAS tool (*Table 2*)[12]. These studies were further analyzed to calculate their likelihood ratio (LR+). This ratio indicates the pre-test to post-test probability to detect the disease[13].

Results

Provisional online database searches found 953 hits. Eighteen original articles met the inclusion criteria. *Figure 1* shows the flow diagram of the studies included for full revision. Ten articles[14-23] described three different potential ultrasonographic diagnostic parameters for DO in adults with OAB symptoms, applying three different approaches. Only one article[24] described a potential ultrasonographic diagnostic parameter for low compliance bladder in adults. Six articles[25-30] described potential biological markers for DO. Finally, one article[31] described experimental non-invasive near-infrared spectroscopy of the bladder for the diagnosis of DO in patients with OAB symptoms.

Only five articles[17-19;22,23] provided diagnostic cut-offs for ultrasonographic parameters. It was possible in four[17-19;23] out of these five articles to calculate the LR+ in our study *(Table 1)*. Two studies[14-15] found no significant difference between cases with DO and controls. Ten studies presented significant correlation between the non-urodynamic and the urodynamic parameters in cases with DO and/or low compliance. Some of them presented significant qualitative or quantitative discrimination between cases and controls. Thirteen studies were conducted on women, one study on men and four studies included both genders.

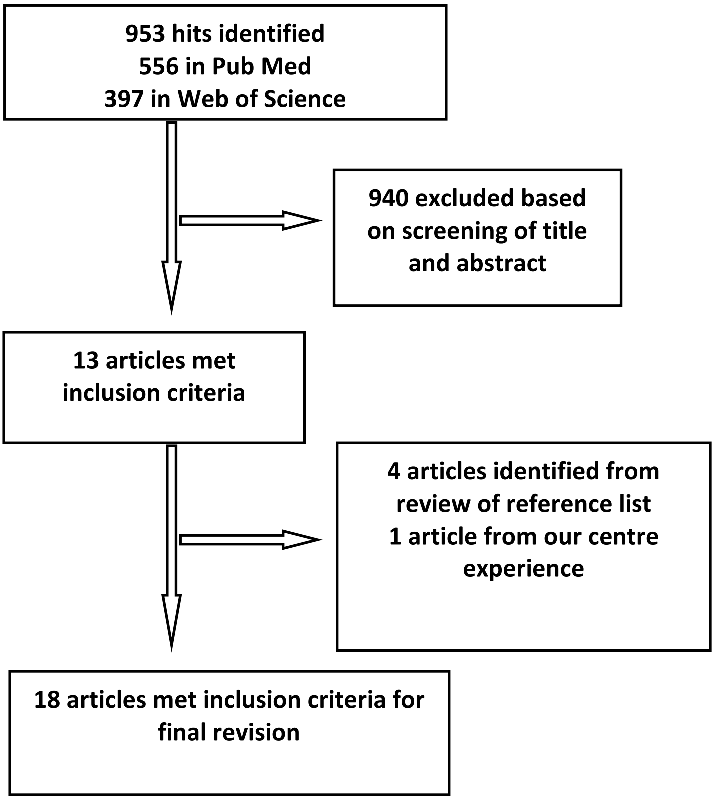

Figure 1: Flow diagram for studies search and inclusion

Ultrasonographic Methods

Bladder wall thickness measurement

Elbadawi *et al.*[32] studied the ultra-structural morphologic changes in bladder wall specimens obtained from patients with bladder outlet obstruction (BOO). The changes were mainly increase in the smooth muscles bulk with or without interstitial collagen deposition. Experimental studies have revealed similar features in animals with bladder outlet obstruction[33]. These findings strengthened the assumption that measurement of the increased bladder wall thickness (BWT) can be used as a diagnostic test for BOO. In urinary bladders with DO, frequent detrusor contractions during the storage phase while the urethral sphincter is closed, are supposed to increase work load on the muscle with consequent hypertrophy[16,19,22,34].

The bladder wall consists of bladder adventitia, which gives a hyperechoic (bright) appearance on ultrasonography, the detrusor muscle layer, which gives a hypoechoic (dark) appearance on ultrasonography, and the innermost layer is the bladder mucosa, which gives a hyperechoic (bright) appearance on ultrasonography[35,36]. If the inner and outer hyperechoic lines were included in the measurement, then BWT is the measured parameter. If measurement skips these two lines, then the detrusor wall thickness (DWT) is the measured parameter.

When an ultrasonographic trans-vaginal (TVUS) approach was applied to measure the BWT of female patients with irritative urinary symptoms, Khullar *et al.*[17] found a significant difference in median BWT between female patients with OAB due to DO, and those without DO (6.3 mm vs. 3.9 mm; $p < 0.001$). A cut-off BWT 5 mm had 84% sensitivity and 89% specificity for DO, while Robinson *et al.*[22] reported a cut-off of 6.0 mm to be highly suggestive of DO.

Applying the same TVUS approach to study BWT in different forms of DO, Serati *et al.*[23] reported significantly thicker BWT in patients with urodynamic 'pure DO' than in patients with other urodynamic diagnoses of urodynamic stress incontinence (USI), mixed incontinence (USI + DO) or normal urodynamics. BWT was 5.22 ± 1.17 vs. 4.37 ± 1.13 mm respectively; $p < 0.0001$. A cut-off BWT of 6.5 mm could identify patients having 'pure DO' with 13.33% sensitivity and 97.67% specificity for DO. The sensitivity of this cut-off BWT declined to 10.9% when it identified women having 'all DO' diagnosis ('pure DO' + 'mixed DO'). This means that applying this cut-off BWT as a screening test, only 10-13% of women with OAB will not undergo further invasive urodynamics.

However, other conclusions were drawn with other techniques. Blatt *et al.*[14] applied trans-abdominal ultrasound (TAUS) to measure the BWT at 200 ml filling volume of the bladder in 180 patients with non-neurogenic voiding dysfunctions. Conventional urodynamics classification of these patients identified 69 as having normal urodynamics, 39 as having BOO, 38 had increased bladder sensations, while 34 patients were diagnosed as having DO. No significant difference in BWT was found between patients with normal urodynamics and those with DO (2.0 mm vs. 1.9 mm respectively; $p = 0.309$).

Detrusor wall thickness measurement

Detrusor muscle has been considered the actual component of the bladder wall that hypertrophies due to the frequent contractions against the high resistance of the bladder outlet complex. A trans-labial ultrasonographic (TLUS) approach was applied to measure the DWT of 686 women with OAB symptoms[19]. Authors reported significant difference in the average DWT between patients with DO (4.7 ± 1.9 mm) and those without DO (4.1 ± 1.6 mm; $p < 0.001$). They suggested various cut-offs for the diagnosis of DO: ≥5 mm, ≥6 mm and ≥7 mm. These cut-offs had a sensitivity of 37%, 22% and 13%, respectively. Having this relatively low sensitivity for DO, authors found none of these cut-offs to be clinically useful as a diagnostic tool for DO.

An interesting study was done by Kuo *et al.*[18] including 25 women with OAB wet symptoms, 28 women with OAB dry symptoms and 28 women free of urinary symptoms as controls. The mean DWT was assessed with both TVUS and TAUS approaches during natural and catheter filling. Authors found no significant difference in mean DWT measured by TVUS among different subgroups of the study (ANOVA $p = 0.243$). The mean DWT was derived from these women applying TAUS approach at bladder capacity and at 250 ml filling. There was no significant difference among the three groups at 250 ml bladder filling, neither with natural filling (ANOVA $p = 0.057$), nor with catheter filling (ANOVA $p = 0.189$). This can be explained by the smaller bladder capacity in patients with wet OAB. However, at bladder capacity, DWT, was significantly higher in patients with urodynamic DO than the urodynamically normal women during both natural filling (1.036 ± 0.397 vs. 0.770 ± 0.209; $p = 0.006$) and catheter filling (0.927 ±

0.407 vs. 0.667 ± 0.184; $p = 0.006$). A cut-off DWT of 0.75 mm at bladder capacity during natural filling had 73% sensitivity and 67% specificity for DO diagnosis. The same cut-off had 73% sensitivity and 50% specificity during catheter filling.

Table 1 shows the results of calculating the LR+ in four studies. Two studies applying TVUS approach presented a cut-off BWT >5 mm [17] and >6.5 mm [23], respectively. Both studies could identify DO in women with OAB symptoms with good LR+ >5. While the other two studies applying TLUS (Lekskulchai and Dietz 535-39 and TAUS)[18] presented a cut-off of 5 mm and 0.75 mm respectively. Both methods had minimal LR+ <2.

Ultrasonographic measurements of BWT and DWT to investigate OAB were performed using devices with various resolutions and zooming powers. Applied approaches were also different in every study. Moreover, filling conditions were different in every study set-up, which may explain part of the discrepancy in results. Oelke *et al.*[37] have proved that DWT decreases significantly between 50 to 250 ml filling. This may hinder the clinical applicability of this method, especially for patients with smaller functional capacity.

These debates were discussed during *The Second World Congress on Controversies in Urology* that was preceded by a web based survey[38]. In that survey 49% of the participants had a positive impression about the role of BWT measurement in the assessment of OAB. However, by the end of the debate session, only 20% of participants were still having the same enthusiasm to reliably apply ultrasonography in the diagnosis of DO. Some suggestions have been made by experts in this field during *The*

International Consultation on Incontinence-Research Society (ICI-RS meeting)[39]. They agreed on the necessity of using digital ultrasound machines with high frequency probes, and to consider the gender difference effect on applying cut-off values of BWT and/or DWT as they are significantly higher in men with BOO than in women or children with the same disorder. Perpendicular imaging was also recommended to avoid over or under estimation. Experts reported no differences when various parts of the bladder wall were addressed during the scan.

We feel that this last recommendation might be argued by the cystoscopic finding in men with BPH/BOO which – sometimes – reveals patchy distribution of bladder trabeculations. This argument might be generalized to BWT and DWT measurement in patients with OAB/DO.
Ultrasonographic measurement of BWT and DWT in the diagnosis of DO is currently a progressing technique with various cut-off values being suggested, especially when the TVUS approach is applied. However, results of various performed studies are inconsistent making the technique universally not yet accepted. On the other hand, although the rational of detecting a potential hypertrophy in bladders with frequent involuntary contractions against a closed sphincter sounds fair, the ultra-structural studies by Elbadawi *et al.*[40] found that the characteristic profile of hypertrophied detrusor muscle cells is absent or only sparse in bladder biopsies from 15 patients with DO.

Although the rational of increased BWT/DWT in men with LUTS/BOO can be accepted, it can be a matter of debate in case of women with OAB/DO. In general, the amplitude of involuntary detrusor muscle contraction is low in women as compared to men. Some women with mixed incontinence and high grades of prolapse might have a relative urethral anatomical kink[16] leading to infravesical obstruction. Therefore, in case of increased BWT/DWT - if any - in these women it needs to be clarified whether this is due to DO or infravesical obstruction.

Some women present with weak pelvic floor muscles making it questionable if they can efficiently contract their pelvic floor muscle during the DO episode.

The concept that DWT is a more specific measure of bladder muscular hypertrophy in case of BOO can be explained by the mechanical theory of contraction against infravesical obstruction. However, the complex etiology, pathophysiology and the substantial contribution of bladder urothelium and sub-urothelial layer in this process cannot be easily ignored. Sub-urothelium is rich in sensory afferents. ATP is one of the purogenic neurotransmitters that stimulate these sensory nerves triggering the overactive detrusor contraction. There is accumulative evidence that ATP is over expressed from urothelium in patients with DO as compared to controls[41].

Ultrasonographic estimation of bladder weight as a predictor for DO in patients with OAB symptoms

Ultrasonographic estimation of bladder weight (UEBW) has previously been proven to correlate with BOO. Kojima *et al.*[36] studied 10 bladder autopsies taken from 10 men in the age of 25-92. After filling of these bladders with 50 to 100 ml of saline, an ultrasonographic scan of the bladders was performed to measure BWT and inner and outer bladder dimensions.

Assuming the bladder to be a sphere, a specific equation was applied. The inner calculated bladder volume was subtracted from the outer total bladder volume. The outcome was multiplied by the bladder specific gravity. Bladder actual weights were measured directly after emptying. Then cross sections were obtained and compared to ultrasonographic measurements. The authors found no difference between the ultrasonographic and the actual BWT. Spherical UEBW correlated with the actual bladder weight ($r = 0.970$; $p < 0.0001$).

One year later, Kojima *et al.* applied this new tool in the non-invasive diagnosis of BOO in men with LUTS. UEBW significantly correlated with pressure flow parameters. It was significantly higher in the obstructed than in the unobstructed group (46.2 ± 13.3 vs. 29.3 ± 9.4 gm; $p < 0.0001$). A cut-off UEBW of 35 gm had 86.2% 'diagnostic accuracy' for BOO[43].

An important fact about the rational of this technique is that the increased BWT in response to BOO can also be expected in case of DO. So a study was performed on 118 women to study the correlation between UEBW and OAB symptoms or urodynamic diagnosis of DO[21]. According to their medical history, patients were classified into three groups to differentiate between women with OAB symptoms, stress urinary incontinence (SUI) or mixed urinary incontinence (MUI) symptoms. Patients were reclassified by conventional urodynamics into 3 categories: category I having DO, category II having SUI and category III having mixed incontinence. The mean UEBW of these women was significantly higher in the OAB group than in the other two symptomatic groups (48 g in the OAB group, 35 g in the SUI group and 40 g in the MUI group; $p < 0.001$). Also it was significantly higher in the DO group than in the other two urodynamic groups (48 g in the DO category, 30 g in SUI category and 45 g in the mixed urodynamic incontinence category; $p < 0.001$) with good inter- and intraobserver agreements.

The rationale of application of UEBW in the assessment of patients with OAB symptoms and those suspected to have DO is theoretically fair. However, it still needs to be investigated on an ultra-structural basis similar to UEBW investigation in BOO studies. UEBW can be affected by severe bladder deformities like diverticulae, which can be expected in neurogenic bladder disorders. More basic investigations are needed to elucidate the pathophysiology of these changes in bladder weight. It should be clear if it is due to DO in these patients, to chronic inflammation of bladder mucosa caused by frequent infections, or both.

UEBW as a predictor of poor detrusor muscle compliance

Follow-up of patients with neurogenic bladder disorders requires repeated filling cystometry to assess the functional performance of the detrusor muscle to guard against upper tract deterioration. This carries the risk of inducing urinary tract infections in these relatively vulnerable patients.

The feasibility of application of UEBW method to evaluate bladder capacity and compliance in these patients was investigated in a study including 25 patients with detrusor areflexia[24]. UEBW correlated significantly with results obtained from conventional urodynamics, cystoscopy and from radiography, as well in terms of bladder deformity and low compliance ($r = 0.56$; $p < 0.01$). A diagnostic cut-off value of 40 g was suggested for high grade bladder deformity with 63% sensitivity and 88% specificity. When the same diagnostic cut-off value was applied for low compliant bladder, it had 100% sensitivity and 95% specificity. On the other hand, it was difficult to prove any correlation between UEBW and vesico-ureteral reflux, which was identified in three patients only.

These results presented UEBW as a potential diagnostic method that might save some invasive follow-up investigations in patients with detrusor areflexia. However, more studies are needed in a larger patients' population to validate this method. It would be more interesting if such studies include patients with both low compliance and/or DO.

Study	Parameter	Approach	Bladder filling at measurement (ml)	With DO (mm)	Without DO (mm)	Significance level	Cut-off (mm)	Sensitivity %	Specificity %	AUC	LR+
Khullar *et al.*[17]	BWT (averaged: trigone, dome, anterior Wall)	TVUS	Post void <50 ml	6.3 (5.3-7.7)	3.9 (3.4-4.5)	P<0.0001	5	84	89	--	7.6
Robinson *et al.* [22]	BWT (averaged: trigone, dome, anterior Wall)	TVUS	Post void <50 ml	6.7 (6-7.4)	5.1 (4.6-5.6)		6	--	--	--	--
Serati *et al.* 23]	BWT (averaged: trigone, dome, anterior Wall)	TVUS	Post void <50 ml	5.22±1.17	4.19±1.14	P<0.0001	6.5	13.33	97.67	0.702 (95% CI=0.64-0.76)	5.8
Blatt *et al.* [14]	BWT (anterior Wall)	TAUS	200 ml	1.9±0.43	2.0±0.53	P=0.309	--	--	--	--	--
Minardi *et al.* [20]	DWT (dome)	TLUS	-	7.1±1.6	4.1±1.1	P=0.019	-	-	-	--	--
Lekskulchai *et al.* [19]	DWT (dome)	TLUS	Post void <50ml	4.7±1.9	4.1±1.6	P=0.001	5	37	79	0.61	1.76
Kuo *et al.* [18]	DWT (anterior wall)	TVUS	Post void <50 ml	4.42±1.4	4.87±1	P=0.243	--	--	--	--	--
		TAUS	At capacity (catheter filled)	0.927±0.41	0.67±0.18	P=0.006	0.75	73	50	0.648 (95% CI=0.49-0.8)	1.46
			At capacity (natural filled)	1.036±0.4	0.77±0.21	P=0.006	0.75	73	67	0.776 (95%CI=0.64-0.91)	1.7

Table 1: Comparison between studies, which investigated the bladder wall thickness (BWT) and/or the detrusor wall thickness (DWT) in the diagnosis of detrusor overactivity (DO). TVUS = trans-vaginal ultrasonography; TAUS = trans-abdominal ultrasonography; TLUS = trans-labial ultrasonography; AUC = area under curve; CI = confidence interval. Results are presented in median with (range) or mean ± standard deviation (SD). LR+ = likelihood ration of positive diagnostic test. (LR+ 1-2 is minimal, LR+ >2 and <5 is moderate, LR+ >5 is good, and LR+ >10 is excellent)[13,42]

	Question	Khullar [17]	Lekskulschai [19]	Kuo [18]	Serati [23]
1	Was the spectrum of patients representative for the patients who will receive the test in practice?	Y	Y	Y	Y
2	Were selection criteria clearly described?	N	Y	Y	Y
3	Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y
4	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Y	Y	Y	Y
5	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Y	Y	Y	Y
6	Did patients receive the same reference standard regardless of the index test result?	Y	Y	Y	Y
7	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Y	Y	Y	Y
8	Was the execution of the index test described in sufficient detail to permit replication of the test?	Y	Y	Y	Y
9	Was the execution of the reference standard described in sufficient detail to permit its replication?	Y	Y	Y	Y
10	Were the index test results interpreted without knowledge of the results of the reference standard?	Y	N/C	Y	Y
11	Were the reference standard results interpreted without knowledge of the results of the index test?	Y	N/C	Y	Y
12	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	N	N	N	N
13	Were un interpretable/ intermediate test results reported?	N/A	N/A	N/A	N/A
14	Were withdrawals from the study explained?	N/W	N/A	N/W	N/W

Table 2: Quality assessment of studies, which present potential diagnostic cut-off for detrusor overactivity (DO). Y= yes; N = no; N/A = not applicable; N/C = not clear; N/W = no withdrawal

Conventional cystometry enables differentiation between these two conditions by observing pressure lines behavior. On the other hand, it is still unclear to what extent ultrasonography can be beneficial in such differentiation. Evaluation of bladder storage function should address some essential parameters, especially when neurological deficit is expected. These parameters are bladder sensation, detrusor activity, bladder compliance and bladder capacity[3]. Moreover, it is of great importance to assess the performance of the urethral sphincter complex and pelvic floor muscles. Again, the current sonographic techniques still cannot present reliable 'surrogates' for these parameters.

Laboratory Biomarkers

Nerve growth factor (NGF) is a signaling protein that induces neuronal differentiation, normally produced by bladder urothelium and smooth muscles[44]. It is produced in higher levels in bladder pain syndrome/interstitial cystitis (BPS/IC)[45]. Kim *et al.* reported significantly higher urinary NGF in men[25] and women[26] with OAB symptoms than controls. A study included 40 women with IC/BPS, 57 women with OAB symptoms and 27 controls[29]. Authors normalized urinary NGF level [pg/ml] by the concentration of urinary creatinine (cr) [mg/dl]. A ratio was developed: NGF/cr. This ratio was found to be significantly higher in patients with urodynamic DO than controls (1.93 vs. 0.09 respectively; p = 0.01). And also higher in patients with IC/BPS than controls (1.35 vs. 0.09 respectively; p = 0.01).

Urinary NGF level was assessed together with DWT in 81 women with OAB symptoms[27]. Patients were classified symptomatically into 28 controls, 28 patients with OAB dry and 25 women with OAB wet. Video-urodynamics classified these patients into 3 subgroups: a group with normal bladders (n = 27), a group with increased bladder sensations on cystometry (n = 30) and a group with DO (n = 22). The urinary NGF levels in OAB wet subgroup were significantly higher than its levels in OAB dry and control subgroups, also it was significantly higher in DO subgroups (55.81 ± 103.03 pg/ml) than in women with urodynamically normal bladders (1.76 ± 4.18 pg/ml; p = 0.09) or those with increased bladder sensations in cystometry (6.21 ± 14.43 pg/ml; p = 0.013). Authors found no significant difference in DWT between all subgroups when measured at fixed bladder volume of 250 ml; they concluded that NGF was superior to DWT as a biomarker for assessment of OAB wet or DO.

NGF can increase in many lower urinary tract disorders such as BOO, prostatitis and interstitial cystitis[46-48]. However, Kuo *et al.* in their comprehensive review of NGF application in urology, think that NGF still can be used as a surrogate biomarker to evaluate the therapeutic outcome in patients with idiopathic or neurogenic DO. They also proposed that some new systemic and local therapeutic lines based on NGF rule in the pathogenesis of DO[49].

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) as an optical technology has been proven by Macnab *et al.*[50] to be capable of non-invasive detection of oxygen dependant hemodynamic changes in the bladder detrusor during voiding. This technology measures the changes in the concentration of bladder wall chromophores, such as oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin

(HHb) relative to baseline. Stothers *et al.*[51] reported NIRS as an independent predictor of BOO with 94% 'precision' in men with LUTS and clinical BPH according to their voiding pattern.

Doppler ultrasound studies revealed significant variations in hemodynamics of the bladder wall during the micturition cycle[52,53] and bladder contractions in animal models[54].

Based on these previous findings, a pilot study was performed. The hypothesis was that involuntary detrusor contractions during a storage phase have specific hemodynamic effects. The objective was to evaluate the feasibility of the non-invasive NIRS of the bladder region to detect these effects.

14 patients with DO were enrolled in this study. All patients had one or more filling cystometry with simultaneous trans-cutaneous NIRS of the bladder region. A total number of 40 DO episodes was obtained. NIRS curves representing O_2Hb, HHb and total hemoglobin (Hb_{sum} [O_2Hb + HHb]) demonstrated significant concomitant deviation from baseline in 37 out of 40 (93%) DO episodes. All onsets of NIRS deviations occurred within the time limit of the DO episodes with a mean delay of 3 seconds (range: 0-9)[55].

After approving the feasibility of this technique, a larger clinical study was performed to evaluate the clinical applicability of NIRS in the diagnosis of DO[31]. Forty-one patients with OAB symptoms underwent 53 filling cystometries with simultaneous NIRS of the bladder. Diagnosis of DO was done according to the ICS guidelines. After exclusion of 28% of the graphs due to motion artifacts, the separated graphs representing both tests were presented to three experienced urodynamicists with three weeks between the first and second presentation.

The graphs showed curves with and without DO episodes where all bladder sensations were marked. The stability was confirmed by stable abdominal pressure curves and extra surface EMG of the abdominal muscles. The urodynamicists marked pressure changes suggestive of DO in the cystometry curves. For NIRS curves they marked definite deviations from baseline.

NIRS curve representing the Hb_{sum} had an average sensitivity of 92% and 72% specificity for DO (AUC: 0.80-0.82; $p < 0.001$). O_2Hb curves had 82% sensitivity and 86% specificity for DO (AUC: 0.80-0.85; $p < 0.001$). The sensitivity and specificity of the HHb curve for DO were 77% and 80%, respectively (AUC 0.73-0.84; $p < 0.001$).

The inter- and intra-observer agreements to identify or rule out the effect of DO on NIRS curves were substantial (kappa >0.6). NIRS curves correlated well with DO episodes detected by conventional urodynamics and were able to detect the hemodynamic changes caused by detrusor contractions. This implies that NIRS can be used to study the regulatory mechanisms of blood perfusion to the bladder during filling as well as the hemodynamic phenomenon of DO.

This real time feature of NIRS is unique in comparison to other non-invasive diagnostic techniques that are examined for DO[15,17]. It can be a potential non-invasive diagnostic tool for DO in patients with OAB symptoms.

Conclusions

Ultrasonographic parameters, such as BWT, DWT and UEBW, have been examined in patients with storage disorders as surrogates for DO in patients with OAB. Only few studies could present potential diagnostic cut-offs for DO. TVUS seems to be a better approach to measure BWT. However, standardization of methodology is still needed.

Laboratory biomarkers, such as NGF, show substantial correlation with DO/OAB, but are still lacking a plausible specificity for DO. NIRS detects the hemodynamic changes caused by involuntary detrusor contractions in real time, but its liability to motion artifacts still limits its clinical applicability. So far, all these techniques still have limitations and cannot be applied reliably in routine clinical practice. None of these methods can quantify other important parameters of bladder storage function than DO. Filling cystometry remains the current gold standard tool in the diagnosis of bladder storage disorders.

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CHAPTER 2

Feasibility of Non-Invasive Near-Infrared Spectroscopy to Diagnose Detrusor Overactivity

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Abstract

Introduction

Near-infrared spectroscopy (NIRS) is an optical technology able to detect the hemodynamic changes in biologic tissues. Our objective was to determine the feasibility of applying NIRS in the non-invasive diagnosis of detrusor overactivity (DO).

Patients and Methods

A comparative analysis was performed on 39 involuntary detrusor contractions (IDC) from 23 filling cystometries with simultaneous non-invasive NIRS of the bladder in 14 patients with DO. Motion artifacts were checked for via surface EMG of the abdominal muscles.

Results

Thirty-nine IDC were obtained. The median amplitude of rise in detrusor pressure at DO was 48 cm H_2O (range: 5-219). The median filling volume at DO was 148 ml (range: 9-531). NIRS curves demonstrated apparently significant deviations from baseline in 35 of 39 DO episodes (90%). All onsets of NIRS deviations occurred within the time period of IDC with a mean delay of 3 s (range: 0-9).

Conclusions

NIRS can be a potential tool for the non-invasive diagnosis of DO.

Feasibility of Non-Invasive NIRS to Diagnose Detrusor Overactivity

Introduction

Overactive bladder (OAB) syndrome is highly prevalent in Western countries. It affects 16.6% of adults >40 years of age in Europe[1]. Filling cystometry is the current standard urodynamic test employed in the diagnosis of detrusor overactivity (DO) in patients with OAB symptoms[2]. However, it is invasive and may cause patient discomfort and urinary tract infection[3].

Near-infrared spectroscopy (NIRS) is an optical technology. It enables the non-invasive monitoring of hemodynamic changes in biological tissues via measurement of the relevant changes in the concentration of tissue chromophores. The chromophores are naturally occurring compounds such as oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (HHb). These two NIRS parameters measure the oxygen supply and consumption of the tissue, respectively. The sum of both parameters (Hb_{sum}) represents the total blood perfusion of the tissue under monitoring[4].

The micturition cycle is associated with substantial variations in the blood flow to the urinary bladder; bladder filling causes an increase in the blood perfusion to the bladder wall. Blood flow decreases at the maximum capacity, and then shows a rebound increase after emptying[5]. Anderson *et al.*[6] reported an increase in bladder wall blood perfusion during evoked bladder contractions. Azadzoi *et al*.[7] reported a marked decrease in bladder wall perfusion during both spontaneous and evoked bladder contractions in animals. NIRS was applied in classification of men with LUTS due to bladder outlet obstruction (BOO) according to their voiding patterns.

The authors reported NIRS as a good predictor of BOO with 88% specificity and 94% 'precision'[8].

Our hypothesis was that involuntary detrusor contractions (IDC) during filling of the bladder have specific hemodynamic effects that can be detected by an imaging technology like NIRS. Our objective was to evaluate the feasibility of the non-invasive transcutaneous NIRS of the bladder to detect these hemodynamic effects during filling cystometry.

Patients and Methods

Patients

Fourteen patients with DO were included in this exploratory study. Patients with gross hematuria and scars from previous bladder surgeries were excluded. The study was approved by the local ethical committee.

Procedure

A dipstick urinalysis was done to exclude UTI and hematuria. Filling cystometry (Solar™; Medical Measurement Systems, Enschede, The Netherlands) started with the insertion of a double lumen gas-filled urethral catheter of 6 Ch for intravesical pressure monitoring. Abdominal pressure was monitored using a rectal balloon. Water was infused10-50 ml/min at room temperature.

Simultaneous with filling cystometry, trans-cutaneous non-invasive monitoring of the bladder region with NIRS was performed (URO-NIRS™; Urodynamix Technologies Ltd, Vancouver, BC, Canada). An emitter and a photo-receiver diode were connected to a rubbery self-adhesive patch. The NIRS optodes were placed directly on the abdomen, 2 cm above the pubic symphysis across the midline[9]. Patients were asked to limit their movements and to avoid straining or urine withholding, especially at the moment of urgency due to DO. During the session, surface EMG monitoring of the abdominal wall muscles was performed to detect any motion artifacts. Data from NIRS were imported in a specially designed urodynamics database for automatic synchronization.

Statistical Methods

Comparative analysis of cystometry curves and their relevant NIRS curves was performed by two experienced urodynamicists. The urodynamicists marked pressure changes in cystometry curves indicative of DO according to the International Continence Society guidelines. Then they looked at the relevant NIRS curves (HHb, O_2Hb and Hb_{sum}) to detect significant visible deviations from baseline concomitant with the IDC. A Mann-Whitney U test was applied to measure the differences between groups.

Results

Urodynamic cystometry registrations from 14 patients with DO were included in the study. The mean age was 65 years (range: 38-79). The mean BMI was 27 kg/m^2 (range: 21–33). All patients underwent one or more filling cystometries with simultaneous non-invasive trans-cutaneous NIRS of the bladder.

Twenty-three filling sessions with a total of 39 IDC were obtained. Each IDC was considered as an individual case for final analysis. The median bladder filling volume at the start of IDC was 148 ml (range: 9-531). The median maximum amplitude of rise in detrusor pressure curves from baseline to peak at IDC was 48 cm H_2O (range: 5-219). The absolute deviation from baseline in NIRS curves was apparently significant in 35 of 39 (90%) HHb curves. The same was true for 34 of 39 (87%) O_2Hb curves and for 35 of 39 (90%) Hb_{sum} curves. All onsets of NIRS deviations occurred within the time period of IDC, with a mean delay of 3 s (range: 0-9). Examples are shown in *figures 1-3*.

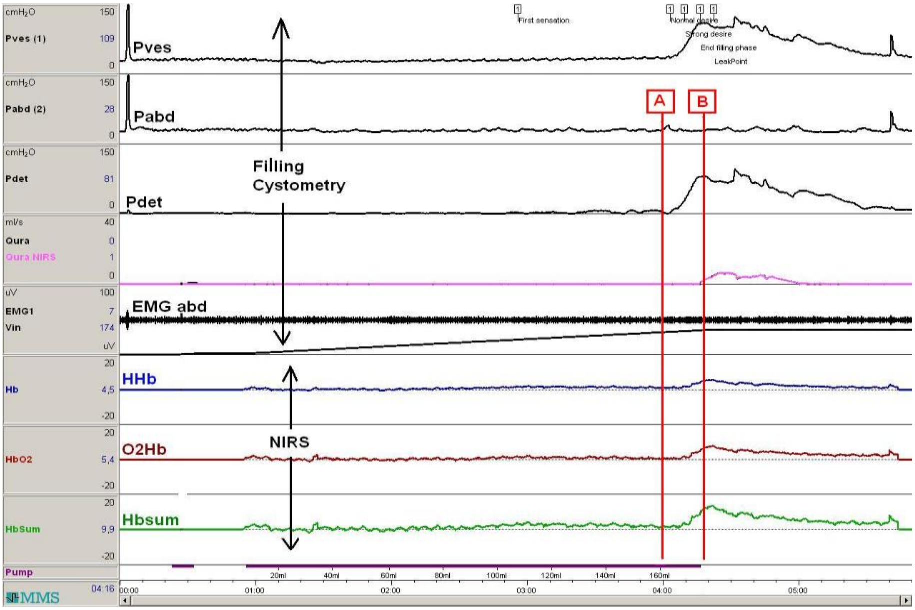

Fig. 1. An example of DO episode with no abdominal activity. An episode of DO as detected by cystometry (upper graph) and NIRS (lower graph). The lower graph shows an initial upward slope of Hb_{sum}, O_2Hb, and HHb curves concomitant with the start of DO (point A) until the peak of DO (point B), followed by sustained downward slope in all NIRS curves till the end of DO episode. Notice the stability of abdominal pressure (P_{abd}) curve.
P_{ves} = intravesical pressure; EMG_{abd} = EMG monitoring of the abdominal wall muscles; P_{det} = detrusor pressure.

For analysis, true positive cases were identified as the cases where at least two thirds of the NIRS curves were positive at IDC. The false negative cases were identified as the cases where at least two thirds of the NIRS curves were negative at IDC. *Table 1* shows the results of a comparison of BMI of the patients, amplitude of rise in detrusor pressure at the peak of IDC, and the bladder filling volume at the start of IDC between both groups.

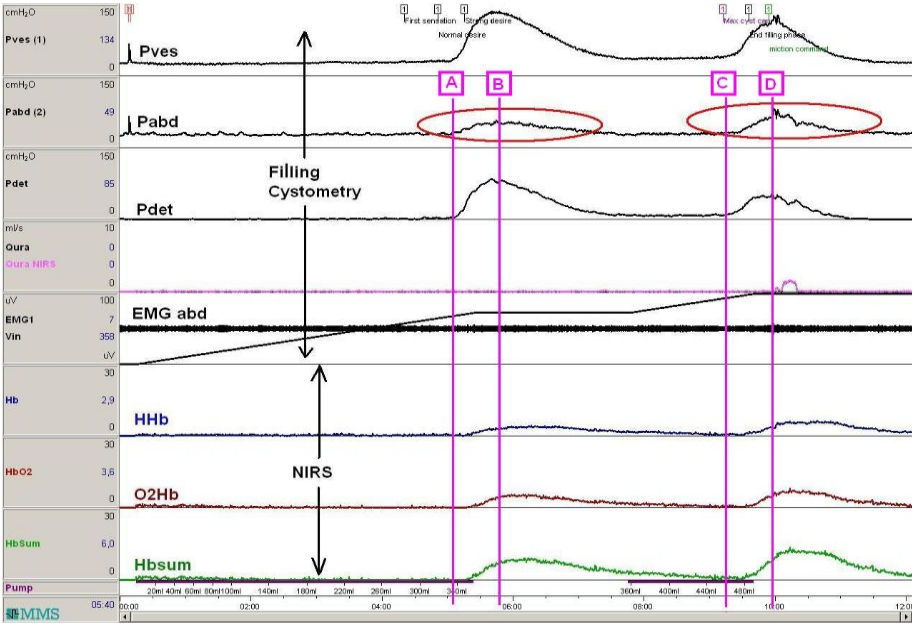

Fig. 2. An example of DO with potential artifact. Two consecutive DO episodes as detected by cystometry (upper graph) and NIRS (lower graph). Abdominal pressure (P_{abd}) curve shows smooth straining pattern as the patient was straining during the 2 episodes. The lower graph shows an upward slope of all NIRS curves concomitant with the start of DO (points A and C) until the peak of DO (points B and D), followed by a sustained but slower and less remarkable downward slope in NIRS curves until the end of DO episode. The second episode was followed by voiding. The P_{abd} curve shows straining pattern concomitant with DO (encircled in red). P_{ves} = intravesical pressure; EMG_{abd} = EMG monitoring of the abdominal wall muscles; P_{det} = detrusor pressure.

Twenty-five of the 35 IDC with significant deviations in NIRS curves occurred at filling volumes less than 200 ml (range: 9-531).

Abdominal pressure curves and/or the surface EMG monitoring of the abdominal wall muscles curves detected straining patterns and/or motion artifacts in 11 of the 35 IDC with concomitant deviation in NIRS. None of the 4 IDC with no concomitant deviation in NIRS curves had any straining patterns and/or motion artifact. NIRS curves demonstrated significant deviations from baseline in 34 occasions. These deviations were concomitant with abrupt movements or cough while detrusor pressure curves were stable (false-positive deviations).

Table 1. Comparison of the relevant demographics and cystometric parameters between the detrusor overactivity (DO) episodes with and without significant deviations in near-infrared spectroscopy (NIRS) curves.

	Cases (n = 14 patients; n = 39 DO episodes		Mann-Whitney U test (95% CI) p value
	true positives (n=10 patients; n=35 graphs)	false negatives (n=4 patients; n=4 graphs)	
Mean BMI	26 ± 4 (20-33)	28±2 (27-31)	0.68
Median filling volume at DO, ml	150 (9-531)	146 (29-174)	0.25
Median amplitude of contraction at DO, cm H_2O	50 (5-219)	15 (5-51)	0.08

Discussion

Doppler flow studies revealed substantial hemodynamic changes in the bladder wall during the micturition cycle[5]. We studied the feasibility of applying the non-invasive optical technology, NIRS, for detection of the hemodynamic effect of IDC in patients with OAB syndrome. The assumption is that NIRS detects the changes in oxygen supply and oxygen consumption of the bladder wall during the IDC.

In order to be able to use NIRS for this detection process, some potential obstacles that could hinder valid NIRS detection should be looked at.

The first obstacle is that the bladder can be anatomically out of reach of the NIRS imaging scale due to the abdominal wall being too thick in some patients. The second obstacle is that NIRS of the bladder is performed early during filling cystometry while the bladder is still empty. The third obstacle is the expected movement of the bladder wall on changing from the flaccid to the contracting form, which might affect the NIRS measurements. Another potential obstacle is low IDC amplitude.

Feasibility of Non-Invasive NIRS to Diagnose Detrusor Overactivity

The last obstacle is the susceptibility of NIRS technology to motion artifacts[10]. NIRS curves demonstrated apparent significant deviation from baseline concomitant with the start of IDC in 35 of 39 (90%). Interestingly, all deviations occurred within the time period of the IDC. This shows the high ability of NIRS to detect the hemodynamic effect of IDC.

Four out of 39 IDC had no concomitant change from baseline in NIRS curves. We looked for the anatomical factors that might cause the bladder to lie out of reach of the NIRS imaging scale, such as morbid obesity or small bladder filling volumes. All four IDC without significant deviations in NIRS curves occurred at a filling volume <200 ml. However, 25 of 35 IDC with significant deviations in NIRS curves occurred at filling volumes <200 ml. This means that NIRS is able to monitor the bladder at relatively lower volumes than expected. The mean BMI was not significantly higher in patients who had IDC with no concomitant deviations in NIRS curves, as compared to those who had IDC with positive concomitant deviations in NIRS curves (28 vs. 26 kg/m^2 respectively; $p = 0.25$).

The median maximum amplitude of a rise in detrusor pressure curves in IDC without significant deviations in NIRS was lower than in those with significant deviations (15 cm H_2O vs. 50 respectively; $p = 0.08$). Although this was not statistically significant, we assume that this might be a cause of false negative outcomes. The reason for not being statistically significant might be explained by the small sample size in our pilot study and the small number of IDC with no concomitant NIRS deviations as compared to those with positive deviations (n = 4 vs. 35 episodes, respectively). More and bigger studies are needed to explore those factors that affect the sensitivity and specificity of NIRS for IDC. Further studies should explore the reproducibility and accuracy of NIRS in clean data set, i.e. without motion artifacts. Then trials to design a clinical diagnostic setup of the technique in real practice are recommended. For these steps, cystometry should be the reference standard.

In our exploratory series, NIRS could identify 90% of IDC via detection of their concomitant imprint on NIRS signals. The effects of IDC on NIRS signals might be explained by one of three possibilities. The first possibility is an autogenic hemodynamic phenomenon of IDC. The second possibility is a compressive pattern of bladder wall vessels due to the sudden contraction during IDC. The last possibility is an expected movement of the whole bladder wall with its vascular content during the IDC, leading to substantial change in the volume of blood crossing the imaging scale of NIRS.

A few non-invasive techniques have been tested to replace the standard invasive filling cystometry for the diagnosis of IDC. These techniques focused on investigating some proxy parameters of IDC, such as sonographic measurement of bladder wall thickness[11], or measurement of urinary nerve growth factor[12]. However, none of these techniques can detect the IDC in real-time. NIRS parameters are presented as graphic display, this advantage enables the bladder monitoring simultaneous with filling cystometry. Hence, for the first time it was possible to detect the IDC in real-time with a new non-invasive technique, comparable to conventional cystometry.

To check for the presence of motion artifacts in NIRS curves, we used the extra surface EMG monitoring of the abdominal wall muscles. Eleven of the 35 IDC with concomitant deviations in NIRS curves had motion artifacts, either due to change in patient position during the session, or due to their efforts to withhold urine at moments of urgency during the IDC. Patient stability and algorithms to cancel motion artifacts in NIRS[13] can be recommended to improve the set-up and measurements in further studies.

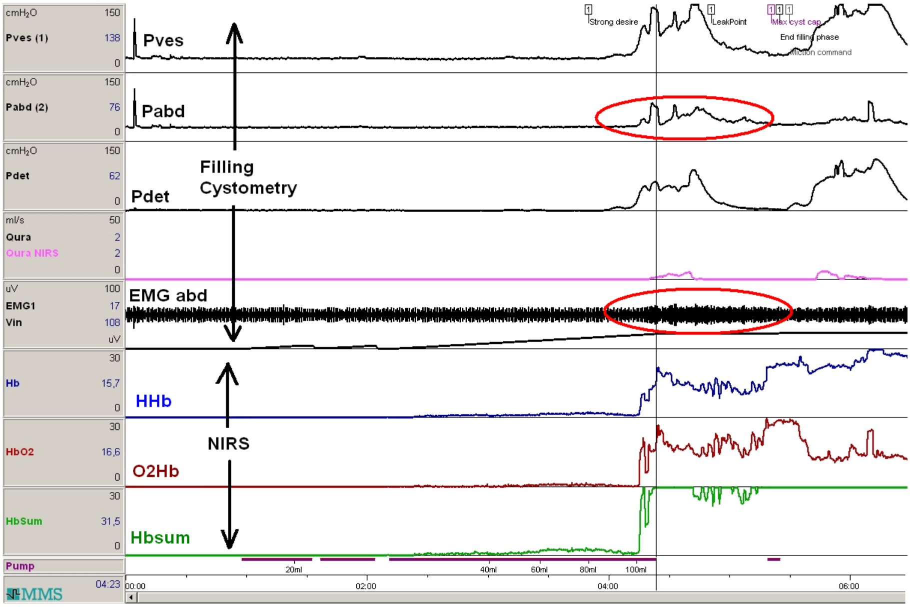

Figure 3. An example of DO with definite motion artifacts. Abdominal pressure (P_{abd}) and EMG monitoring of the abdominal wall muscles (EMG_{abd}) curves show irregular abdominal activity pattern concomitant with DO (encircled) because the patient unexpectedly changes his positions by leaning forward. The NIRS part of the graph shows an abrupt, sharp, irregular, upward slope of all NIRS curves concomitant with the start of DO, followed by less remarkable sustained downward slope till the end of the DO episode.
P_{ves} = intravesical pressure curve; P_{det} = detrusor pressure.

Conclusions

NIRS is able to detect the hemodynamic effect of DO. It can be a potential tool for the non-invasive diagnosis of DO. More studies are needed to explore the factors that influence NIRS detection of DO and to evaluate its applicability in clinical practice. If all practical problems are overcome, NIRS could be very valuable, not only in routine clinical practice, but also in studies exploring treatments for OAB and DO.

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CHAPTER 3

Near-Infrared Spectroscopy: a Novel, Noninvasive Diagnostic Method for Detrusor Overactivity in Patients with Overactive Bladder Symptoms – a Preliminary and Experimental Study.

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Abstract

Background

Near-infrared spectroscopy (NIRS) is an optical technology. It detects the hemodynamic changes in tissues via non-invasive measurement of changes in the concentration of tissue chromophores, such as oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb). Involuntary bladder contractions may cause changes detectable by NIRS.

Objective

To address the accuracy and reproducibility of NIRS to detect the hemodynamic effects of detrusor overactivity (DO).

Design, setting, and participants

A prospective cohort study was carried out on 41 patients with overactive bladder symptoms.

Measurements

Forty-one patients underwent one or more filling cystometries with simultaneous NIRS of the bladder. The separated graphs representing both tests were presented to three urodynamicists on two occasions, 3 weeks apart. The graphs showed curves with and without DO episodes with the bladder sensations marked. Thirteen of 47 graphs (28%) with DO and 16 of 58 graphs (28%) without DO were excluded due to motion artifacts. The urodynamicists marked pressure changes suggestive of DO in the cystometry curves. For NIRS curves they marked definite deviations from baseline. The sensitivity and specificity of NIRS for DO were determined. The inter- and intraobserver agreements were determined.

Results and limitations

Valid data from 33 of 41 patients (80%) were included in the analysis. The interobserver agreement to trace the effect of DO on NIRS curves was ‘substantial’ ($k_f > 0.6$). The sensitivity of the Hb_{sum} (O_2Hb + HHb) curves for DO was 62-97% with a specificity of 62-79% (area under the curve [AUC]: 0.80-0.82; $p < 0.001$). O_2Hb curves had 79-85% sensitivity and 82-91% specificity for DO (AUC: 0.80-0.85; $p<0.001$). The sensitivity and specificity of the HHb curves for DO were 71-82% & 77-82%, respectively (AUC: 0.73-0.84; $p < 0.001$). These values represent the performance of NIRS in the data sample that is not contaminated with motion artifacts; they are not representative of a general clinical setting.

Conclusions

NIRS is a potential non-invasive and reproducible, diagnostic method to detect DO.

NIRS: a Novel Diagnostic Method for DO in Patients with OAB Symptoms

Introduction

Overactive bladder (OAB) syndrome is highly prevalent in Western culture[1]. It negatively affects the patient's quality of life[2]. Filling cystometry is the standard urodynamic test to detect detrusor overactivity (DO)[3]; however, it is invasive and may cause patient's discomfort and urinary tract infections (UTI)[4]. Therefore, a non-invasive diagnostic tool that can replace conventional cystometry is recommendable, especially for patients who undergo regular urodynamic evaluation.

Doppler ultrasound studies have revealed significant variations in the blood flow of the bladder wall during the voiding cycle[5,6] and bladder contractions in animal models[7]. DO is assumed to cause substantial variations in oxygen supply and consumption of the bladder wall during involuntary muscle contraction.

Near-infrared spectroscopy (NIRS) as an imaging technology can monitor the hemodynamic changes during bladder filling and voiding. Light in the near-infrared area is capable of penetrating the skin to the underlying tissues and is absorbed by naturally occurring chromophores, such as oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb). NIRS enables detection of oxygen-dependant hemodynamic changes in biologic tissues by measurement of the relevant changes in the concentration of tissue chromophores relative to baseline. Total hemoglobin (Hb_{sum}) is an indicator of total blood perfusion that can be derived from the sum of O_2Hb and HHb[8].

Urologic applications of NIRS cover various urologic disorders[9]. NIRS was previously reported to be an independent predictor of bladder outlet obstruction (BOO) with a good correlation between NIRS and pressure flow parameters[10].

Previously, we showed that transcutaneous NIRS of the bladder is feasible to detect DO episodes as the involuntary detrusor contractions have characteristic imprints on NIRS signals[11]. The objective of this study was to determine the accuracy and reproducibility of NIRS during cystometry in detecting DO episodes. Therefore, the sensitivity and specificity of NIRS changes compared to cystometry were investigated after exclusion of NIRS data contaminated with motion artifacts. Moreover, the inter- and intraobserver agreements of DO diagnosis in NIRS curves were determined.

Patients and methods

Patients

The study group consisted of 41 consecutive adult patients referred to the Radboud University Nijmegen Medical Centre, The Netherlands for urodynamics between 20 August and 28 December 2009. Inclusion criteria were men or women ≥18 years old with urgency with or without incontinence, frequency and nocturia. Exclusion criteria were abdominal scars, hematuria and a history of mixed incontinence. One patient was diabetic and one was treated for hypertension. Antimuscarinics were stopped ≥3 days before urodynamics. This study was approved by the local ethics committee.

Procedure

Patients completed a 24-hour voiding diary. Patients with clinical benign prostatic hyperplasia (BPH) and voiding symptoms suggestive of BOO completed an International Prostate Symptom Score (IPSS) questionnaire.

Urinalysis was performed to exclude UTI and hematuria. All patients underwent cystometry (Solar™, Medical Measurement Systems, Enschede, The Netherlands). A gas-filled urethral catheter (6 Fr/Ch) was inserted to monitor intravesical pressure (P_{ves}), while abdominal pressure (P_{abd}) was monitored using a rectal balloon. Water was infused at room temperature with filling rates of 10-50 ml/min as requested by the patient's physician. The same rate was used when several cystometries were performed in the same patient.

Transcutaneous, non-invasive bladder monitoring with NIRS (URO-NIRS, Urodynamix Technologies Ltd, Vancouver, Canada) was performed simultaneously with cystometry. An emitter and a sensor were connected to a rubbery self adhesive patch, 4 cm apart. The patch was placed on the abdomen 2 cm above the pubic symphysis across the midline[12].

Baseline NIRS reading for 30 s was followed by testing the effect of cough and Valsalva maneuver on NIRS signals. Patient movements, straining and urine withholding were restricted. Surface electromyogram (EMG) monitoring of the abdominal wall muscles (EMG_{abd}) was used to rule out motion artifacts. Bladder sensations and events were recorded.

The cystometries were diagnosed by a urodynamicist according to the International Continence Society guidelines to identify patients with and without DO. NIRS data were imported and automatically synchronized in the urodynamics database. Graphs contaminated with motion artifacts were excluded (*figure 1*). For rating purposes, the cystometry graphs and NIRS graphs were separated and coded. Graphs with DO were used as cases (*figure 2*) and graphs without DO as controls.

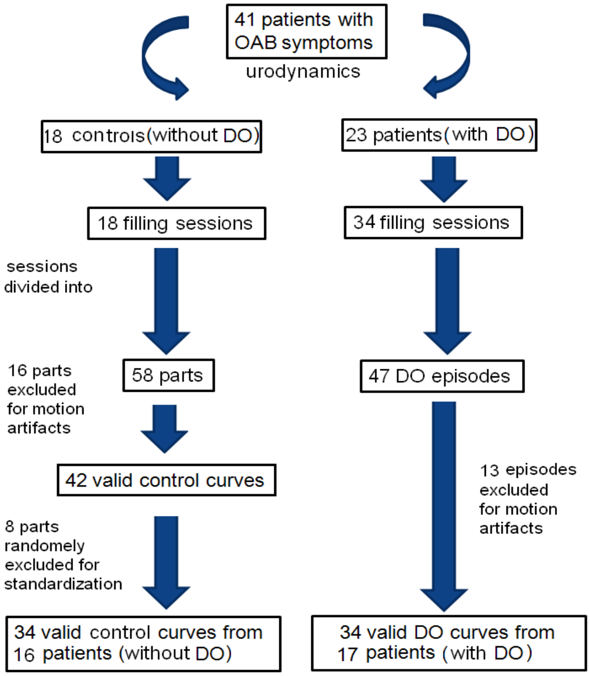

Fig. 1 – The method followed in deriving graphs representing cases of detrusor overactivity (DO) and controls.
OAB = overactive bladder.

Inter- and intraobserver variability

The cystometry graphs consisted of three curves representing Pves, Pabd, and Pdet. NIRS graphs consisted of three curves representing HHb, O2Hb and Hbsum. Flowmetry and EMGabd curves were added to the cystometry and the NIRS graphs.

Rating was done by three experienced urodynamicists on two occasions 3 weeks apart. The cystometry graphs and the NIRS graphs were presented separately and randomly to the raters. The raters did not know which NIRS graph belonged to which cystometry graph. The urodynamicsts had to look for pressure changes suggestive of DO for the cystometry graphs and definite deviations from baseline in each NIRS curve (O_2Hb, HHb and Hb_{sum}).

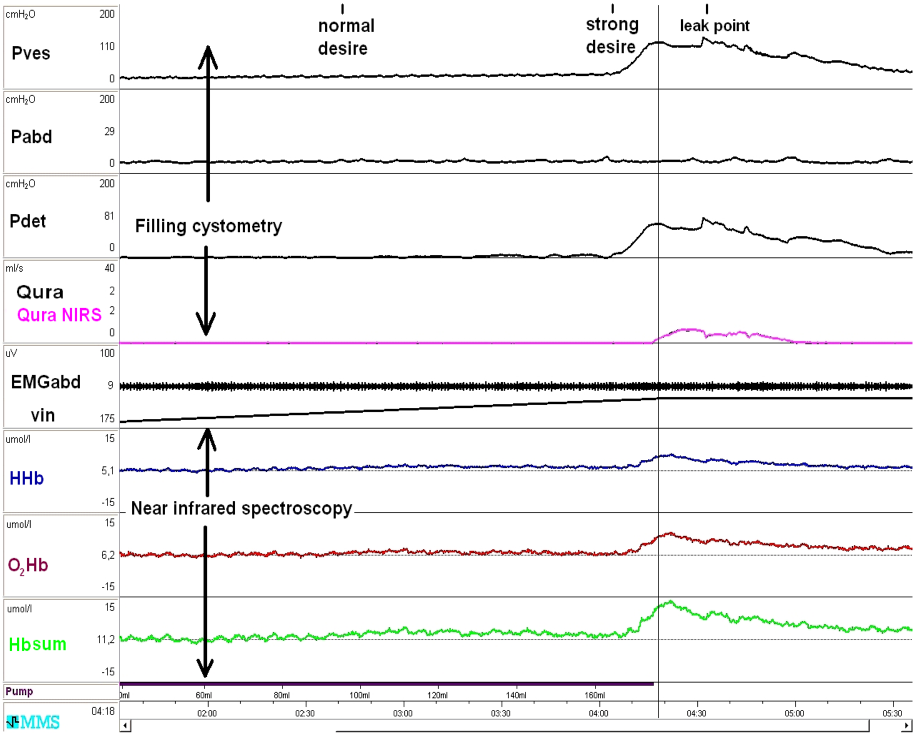

Fig. 2 – Detrusor overactivity (DO) as detected by cystometry and near-infrared spectroscopy (NIRS).Part of the cystometry (upper part) with simultaneous NIRS bladder monitoring (lower part) of a 69-yr-old male patient who presented with OAB symptoms showing the hemodynamic effects of DO represented by relative NIRS changes. An initial upward slope of oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) curves, and of the curve representing the sum of both (Hb_{sum}) is seen concomitant with the start of DO as evidenced by sudden increase in detrusor pressure (P_{det}) curve with urine leakage. This initial hyperemia was followed by sustained downward slope in all NIRS curves until the end of DO episode.
P_{ves} = intravesical pressure; P_{abd} = intraabdominal pressure; Qura = flow rate; EMG_{abd} = abdominal electromyogram; vin = volume of fluid infused in the bladder.

Statistical method

The intra- and interobserver agreements were analyzed using Cohen's Kappa (k_c) and Fleiss' Kappa (k_f) statistics[13]. Kappa values were interpreted based on the convention by Landis and Koch: <0, no agreement; 0-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.0, almost perfect agreement[14]. Receiver operating characteristic curves were used to determine the diagnostic value of NIRS in predicting DO. The Mann Whitney U test was used for differences between groups.

Results

This study included 34 men and 7 women (mean age: 62 ± 14 year) with overactive bladder (OAB) symptoms. The mean body mass index was 26 kg/m^2 (range: 20–33). Seventeen patients had neurogenic disorders, 21 men BPH and 3 idiopathic OAB. The mean frequency was 12 ± 3 voids per day (range: 6–17).The mean IPSS was 17 (range: 5–33) for patients with BPH. Fifty-two cystometry sessions with simultaneous NIRS were performed. The cystometries identified 23 patients with DO who underwent 34 cystometry sessions. Forty-seven DO episodes were identified. To get the optimal NIRS graphs, only 34 of 47 DO graphs were selected for the final analysis based on the stability of P_{abd} and EMG_{abd} curves. Each DO episode was considered as an individual case. The median bladder filling at the start of DO episodes was 137 ml (range: 12-492 ml). The median P_{det} change at DO was 42 cm H_2O (range: 6-215 cm H_2O).

Cystometry identified 18 patients (one cystometry each) without DO. Their data were used for control purposes. Each control cystometry session was divided into equal parts, which included sensation marks. A total of 58 control graphs were obtained of which 16 (28%) were excluded based on the stability of P_{abd} and EMG_{abd}. Thirty-four of the remaining 42 graphs were randomly selected as individual control cases using SPSS (SPSS Inc, Chicago, IL, USA).

Table 1 shows the results of the two rating sessions. The overall diagnostic agreement for the three observers was 92% for cystometry graphs (k_f = 0.84). For the NIRS, the observers agreed on 81% of the HHb curves (k_f 0.63), 84% of the O_2Hb curves (k_f = 0.69) and 81% of the Hb_{sum} curves (k_f =

0.61). The AUC value ranges for the diagnostic performance of NIRS for the three observers were 0.73-0.84 for HHb, 0.80-0.85 for O_2Hb and 0.80-0.82 for Hb_{sum} ($p < 0.001$). The intraobserver agreement for cystometry was k_c = 0.85-0.97 and for NIRS, k_c = 0.53-0.79 for HHb, 0.65-0.76 forO_2Hb and 0.67-0.75 for Hb_{sum}. The sensitivity of NIRS for DO, as an average of the three observers, was 92% for Hb_{sum}, 82% for O_2Hb and 77% for HHb.

The specificity was 86% for O_2Hb, 80% for HHb and 72% for Hb_{sum}. However, it should be mentioned that these high values do not represent the actual sensitivity and specificity in a general clinical setting, but only in an optimal study sample (72%) not contaminated with motion artifacts. The performance of NIRS would have been lower if analysis of the whole group, including motion artifacts, was done.

Table 1– Results of the two rating sessions*

Patients, n = 34		Session I				Session II			
		Cy. %	HHb %	O_2Hb %	Hb_{sum} %	Cy. %	HHb %	O_2Hb %	Hb_{sum} %
Observer 1	Cases	100	82	85	97	10 0	82	88	97
	Controls	9	18	18	38	9	23	21	53
Observer 2	Cases	100	71	79	88	97	68	65	73
	Controls	21	23	9	26	9	26	9	38
Observer 3	Cases	100	79	82	91	97	62	62	65
	Controls	0	18	15	21	0	18	18	21

Cy = Cystometry; HHb = deoxyhemoglobin; O_2Hb = oxyhemoglobin; Hb_{sum} = total hemoglobin

* The ratio of the graphs rated with the answer ‘yes’ to the total number of detrusor overactivity graphs in the upper row (true positives) and the ratio of the graphs rated with the answer ‘yes’ to the total number of control graphs in the upper row (false positives) are shown for each observer. The columns in the table represent the results of rating the cystometry and the individual near-infrared spectroscopy curves, respectively, during the two rating sessions.

Table 2 – A comparison of some relevant demographic and urodynamic parameters between the true-positive and false-negative cases based on near-infrared spectroscopy diagnosis.

	Cases, n = 17, 34 DO episodes		*p* value*
	True positives n = 14 patients, 29 graphs	False negatives n = 3 patients, 5 graphs	
Mean BMI ± SD (range)	25.8 ± 3 kg/m^2 (20.5-31)	25.4 ± 4 kg/m^2 (20.8-28.4)	0.63
Median filling volume at DO, ml (range)	131 (12-492)	149 (59-171)	0.51
Median peak pressure at DO, cm H_2O (range)	47 (11-215)	20 (6-24)	0.004

DO = Detrusor Overactivity; BMI = Body Mass Index; SD = standard deviation. * Mann Whitney U test.

To rate false-positive and false-negative DO diagnosis in NIRS graphs, only graphs with at least two curves marked with a deviation were counted as positive. Although 16 of 58 control graphs (28%) were excluded for motion artifacts, the NIRS graphs were rated falsely positive in 6 of 34 (18%) controls. The NIRS curves showed no deviation in 5 of 34 (15%) DO episodes. The median change in P_{det} at DO was significantly lower in these false-negative cases as compared to the true-positive cases (20 vs. 47 cm H_2O; $p < 0.005$) (*table 2*). Twenty of 29 true-positive cases had DO at a filling volume <100 ml, while 1 in 5 false-negative cases had DO at a volume <100 ml. No adverse events related to NIRS occurred.

Discussion

This is the first clinical study that tests the application of NIRS during the filling phase of the voiding cycle. Our objective was to determine the accuracy and reproducibility of NIRS in detecting DO episodes during cystometry.

NIRS: a Novel Diagnostic Method for DO in Patients with OAB Symptoms

Cystometry detects the mechanical effect of DO. NIRS is used to measure the changes in concentration of bladder wall chromophores relative to baseline in response to bladder events. The assumption is that changes in activity and consequent oxygen consumption cause chromophore changes. This real-time feature of NIRS is unique in comparison to other non-invasive diagnostic techniques that are examined for DO[15,16].

There are three possible reasons that can explain the characteristic imprint of DO on NIRS signals. The first possibility is an auto-regulatory hemodynamic mechanism in the bladder. The second possibility is the mechanical compressive effect of DO on the bladder wall vasculature. The third possibility is the effect of bladder wall movements during DO, leading to momentary changes in blood volume lying within the NIRS imaging scale. High inter- and intraobserver agreements are mandatory for assessment of the clinical applicability of any new diagnostic test. Agreement among the urodynamicists was 'almost perfect' for cystometry, while it was 'substantial' for NIRS (K_f = 0.84, 0.61, 0.69, and 0.63 for cystometry, Hb_{sum}, O_2Hb, and HHb curves, respectively). This might be explained by the familiarity of the urodynamicists with the classic setup of the conventional cystometry.

NIRS curves had a good diagnostic performance as predictors of DO, giving a range of AUC values of 0.80–0.85 for O_2Hb curves, 0.73–0.84 for HHb curves and 0.80–0.82 for Hb_{sum} curves, as calculated for the three observers. NIRS was highly sensitive to detect DO episodes: 92% for Hb_{sum}, 82% for O_2Hb and 78% for HHb. Hb_{sum}, curve being the sum of O_2Hb and HHb, can explain its higher sensitivity for DO.

NIRS is susceptible to motion artifacts[17]. In order to have NIRS applied reliably, artifacts should be avoided. *Figure 3* shows the imprint of cough and Valsalva's maneuver on NIRS. Therefore, 28% of the graphs were

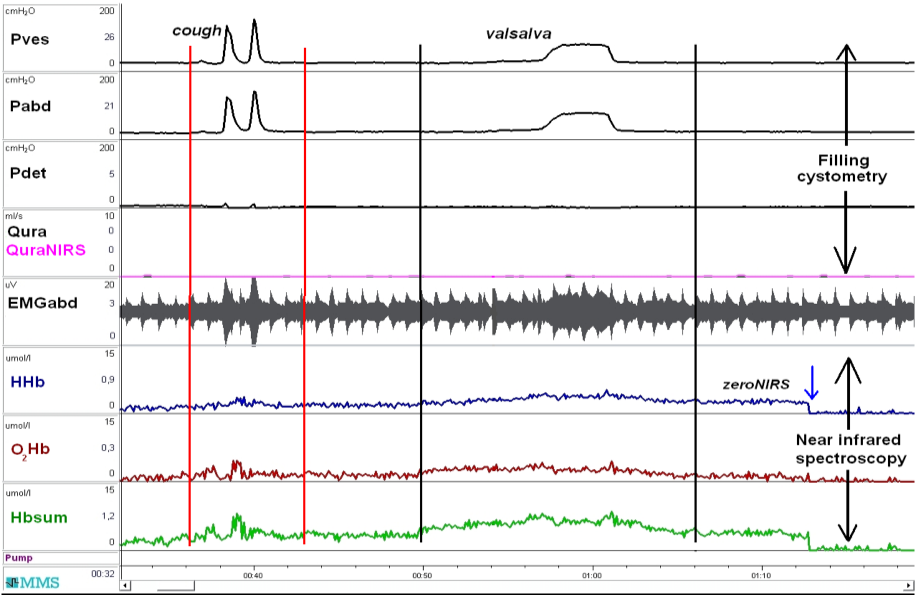

Figure 3– Effect of cough and Valsalva's maneuver on near-infrared spectroscopy (NIRS) curves and abdominal electromyogram (EMG_{abd}) when tested at the beginning of the filling session. Cough causes sharp rise in all NIRS curves and EMG_{abd} (between the two vertical red lines). Valsalva's maneuver leads to a slower and more sustained rise in NIRS curves (between the two vertical black lines). The NIRS changes started earlier than the actual rise in abdominal pressure because the patient leaned forward prior to straining. The blue arrow points to re-zero NIRS to normalize all NIRS parameters before filling starts.
P_{ves} = intravesical pressure; P_{abd} = intra-abdominal pressure; Qura = flow rate; O_2Hb = oxyhemoglobin; HHb = deoxyhemoglobin; Hb_{sum} = O_2Hb + HHb.

excluded from analysis. The overall specificity of NIRS parameters for DO was 86% for O_2Hb, 80% for HHb and 72% for Hb_{sum}. There were six false-positive cases out of the 34 control graphs. This implies that observers still see some deviations in NIRS curves in absence of DO. One explanation could be a DO episode that was not detected by cystometry. Radley *et al.* found that conventional cystometry classified only 32 of 106 women with

OAB symptoms as having DO, while ambulatory urodynamics classified 70 women as having DO[18]. Another explanation could be the wash-out effect of accumulated vasodilator substances as part of the regulatory mechanisms to maintain blood perfusion to the bladder wall during filling[19]. A third possibility would be a misinterpretation of the physiologic, systemic, hemodynamic fluctuations of respiratory signals or cardiac pulsations[17]. This is unlikely because normally these fluctuations are regular, rhythmic and of low amplitude.

NIRS failed to identify 5 of 34 cases with DO as compared to urodynamics. Explanations could be a bladder contraction with low amplitude or the bladder lying out of reach of the NIRS imaging scale due to a small bladder volume or a thick abdominal wall. Twenty of 29 true-positives had DO at filling volumes <100 ml, while only 1 in 5 false-negative cases had DO at <100 ml. Only the difference in P_{det} was significant between the false-negative and true-positive cases. Therefore, a bladder contraction with a low P_{det} seems to be the main reason for the false negativity.

Our study has some limitations. More men were included than women, while generally OAB symptoms are more prevalent in women. This can be explained by the high inclusion number of men with BPH. We excluded 28% of the graphs due to motion artifacts. It was mandatory in our methodology to have non-contaminated data in order to evaluate the scientific value of NIRS in the diagnosis of DO. We believe that the sensitivity and specificity were high in our series because they were tested only within a selected data sample. However, the situation should be different when the clinical applicability of NIRS will be addressed. Recently, algorithms were developed for cancellation of motion artifacts[21]. This could be applied to improve future study set-ups.

No laboratory screening was done to exclude systemic vasculopathies.

Conclusions

In the current study, we showed that NIRS is non-invasive and reproducible with high sensitivity for detecting DO. Its value for clinical trials evaluating treatments for DO remains to be determined. NIRS curves correlate well with DO episodes detected by conventional urodynamics. NIRS seems to detect the hemodynamic changes caused by detrusor contractions. This implies that NIRS can be used to study the regulatory mechanisms of blood perfusion to the bladder during filling as well as the hemodynamic phenomenon accompanying DO. NIRS is a potential non-invasive diagnostic tool for DO in patients with OAB symptoms.

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CHAPTER 4

Non-Invasive Techniques in the Diagnosis of Voiding Disorders

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Abstract

Introduction

Pressure flow study (PFS) is the current standard test in the diagnosis of voiding disorders. It is invasive and potentially morbid. Attempts are currently ongoing to develop noninvasive techniques to replace PFS.

Methods

Pub Med and Web of Science searches of the published data on noninvasive diagnostic techniques for bladder outlet obstruction (BOO) in patients with lower urinary tract symptoms (LUTS) were carried out. The pathophysiological and clinical relevance in addition to the diagnostic accuracy of these techniques were scrutinized.

Results

Noninvasive measurement of isovolumetric pressure was able to address the detrusor contractility, but the extent of contribution of abdominal pressure during voiding is still lacking in this method. Non-urodynamic parameters, derived from ultrasonographic methods, such as bladder wall thickness (BWT), detrusor wall thickness (DWT), intravesical prostatic protrusion (IVPP) and ultrasonographic estimated bladder weight (UEBW), have good evidence on an ultra-structural basis and show good correlation to BOO. Standardization of methodologies followed in measuring these parameters will determine their applicability in clinical practice. Other techniques, such as Doppler ultrasound uroflowmetry, perineal noise recording and Doppler resistivity index of the bladder wall, are gaining evidence. More extensive studies are needed to determine the reproducibility of these techniques.

Attempts to combine some of the above-mentioned parameters could improve their statistical performance. However, more clinical value can be obtained by combining parameters sharing common clinical and pathophysiological criteria.

Conclusions

Measurement of the isovolumetric pressure and ultrasonographic derived surrogates of BOO are the most promising for the future of noninvasive diagnosis of BOO. NIRS is unique for its ability to detect the hemodynamic effect of detrusor contraction during voiding in real time. However, its clinical value still needs to be evaluated. None of these techniques has been proven to effectively replace the standard PFS in the diagnosis of voiding disorders.

Non-Invasive Techniques in the Diagnosis of Voiding Disorders

Introduction

Lower urinary tract symptoms (LUTS) are highly prevalent in male population; 62% of men above the age of 40 years old experienced LUTS at least once in their life, 29% of these symptoms were reported during voiding[1]. Voiding LUTS are defined according to the -International Continence Society (ICS) guidelines as hesitancy, slow intermittent stream, straining and terminal dribble. Pressure flow study (PFS) is the current standard urodynamic test for the diagnosis of bladder outlet obstruction (BOO) in patients with voiding LUTS. This test is unique in its ability to estimate the detrusor muscle voiding pressure that plays a pivotal role not only in the diagnosis, but also in surgical decision making in patients with BOO due to BPH. However, the PFS test is invasive, expensive and time consuming. It can also cause discomfort, urinary tract infection (UTI) and hematuria[2].

This review overlooks the existing non-invasive diagnostic tools and appreciates their usefulness as a replacement for conventional urodynamics in the evaluation of lower urinary tract dysfunctions during the voiding phase of the micturition cycle.

For every technique, the index study was presented and then followed by the more recent studies. We focused on the rational implied to address the pathophysiological and clinical relevance of the non-urodynamic parameters derived from these studies.

1. Uroflowmetry

Observation of urine flow provides objective evidence of normality of voiding. Flowmeters are designed on the basis of either a rotation disk or weight transducer mechanisms. Flowmetry includes observation of flow pattern and rate. A normal voiding pattern is a smooth bell shaped curve, while an obstructed void shows a more flattened trace with intermittency. A constrictive urethral obstruction may show a flattened plateau flow pattern. Flow rate, defined as the volume of urine voided through the urethra per time unit, includes many variables. The most frequently used variable is the maximum flow rate (Q_{max}). A Q_{max} below 10 ml/s might indicate BOO[3]. Abrams *et al.*[4] recommended flowmetry to be done routinely in patients undergoing prostatectomy due to BPH because it could be a predictor of good surgical outcome. However, there are many limitations to rely on flowmetry as a single tool in the diagnosis of BOO. An important disadvantage of flowmetry is that it cannot distinguish between BOO and poor detrusor contractility[3,5]. In a multicentre study[6] 1271 men between 45 - 88 years old presented with LUTS and BPH, Q_{max} weakly correlated with patients' symptoms (r = -0.19; $p < 0.001$). A Q_{max} cut-off value of 10 ml/s had a sensitivity, specificity and positive predictive value (PPV) of 47%,70% and 70%, respectively for BOO. Q_{max} show clinically important variations when flowmetry measurements are repeated in the same visit. In a study that included 147 men with LUTS, uroflowmetry was assessed in two visits, twice in each visit, two weeks apart. In the first visit, the intra-individual difference in Q_{max} was 2.1 ml/s between the first and second voids ($p = 0.71$). While in the second visit it was 5.18 ml/s ($p = 0.35$) making single flowmetry measurement questionable, especially when surgical intervention is expected[7]. Therefore, trials were performed to get multiple measurements of flowmetry from one patient. In a study by Reynard[8] 165 men with LUTS were asked to void 4 times in a flowmeter to assess the incremental value of consequent voids. The post-void residual urine (PVR) was also measured. Then, the patients underwent PFS to be classified as obstructed or unobstructed. Four threshold Q_{max} values were suggested as indicators of BOO: <8, <10, <12 and <15 ml/s for void one. Then to the highest value of Q_{max} on voids one and two, voids one to three, and voids one to four. The authors reported significant increase in maximum values of Q_{max} on consequent voids (≥3 ml/s; p = 0.017). Specificity and PPV of Q_{max} for BOO at various thresholds improved on consecutive voids. On the other hand, sensitivity of Q_{max} for BOO showed a steady decrease. Apart from the above-mentioned weaknesses of uroflowmetry to detect BOO, it has to be mentioned that automated maximum flow rate readings are liable for artifacts and may be misleading[3].

Up till now, uroflowmetry can be used as a single screening test to identify patients with LUTS who really need further PFS to establish the diagnosis of BOO, but still cannot replace PFS in such diagnosis.

2. Ultrasonographic methods

2.1. Bladder wall thickness

Voiding against high resistance of the bladder outlet complex is suspected to be a leading cause of increase in the bladder wall thickness (BWT)[9]. Elbadawi *et al.* studied the ultra-structural morphologic changes in bladder wall specimens obtained from patients with BOO. The changes were mainly increase in the smooth muscles bulk with or without interstitial collagen deposition[10]. Accordingly, it was assumed that measurement of the increase in the mean BWT can be used as a diagnostic test for BOO.

The normal range of BWT was investigated in 410 healthy children (1 day-18 years) and 10 adults (19-42 years). The mean BWT was 2.13 ± 0.59 mm. The authors found no significant difference between male and female children (2.19 mm vs. 2.08 mm respectively; p = 0.07)[11]. On the other hand, the mean BWT in healthy adults demonstrated a significant difference between women and men (3.0 mm vs. 3.33 mm; p < 0.003)[12].

BWT decreases with increase in bladder filling[11]. To solve this problem, trials were done to standardize it with regard to different bladder filling volumes. Hence, the bladder wall thickness index (BWTI) was developed[13]. BWT was measured at four sites: floor, dome and the two lateral bladder walls. Longitudinal and transverse inner bladder diameters were also measured. The outcome of the averaged BWT at all points divided by the averaged bladder inner diameters provides the BWTI. The authors suggested a cut-off of 0.13 with 100% sensitivity, 90% specificity and 94% PPV for obstruction (p = 0.0004)

Others measured the BWT at fixed filling volumes. Manieri *et al.*[14] measured the BWT at 150 ml bladder filling in 174 patients. They found that a cut-off value of 5 mm holds a specificity of 92% but with a low sensitivity of 54% for BOO, while BWT strongly correlated with urodynamics parameters in favor of obstruction (r = 0.6; p ≤ 0.0001).

Hakenberg *et al.* reported a BWT of 3.67 ± 0.11 mm in a group of men above the age of 60 years with LUTS and BPH with a significant difference from the other two healthy groups of their study (3.33 ± 0.08 mm for healthy men and 3.05 ± 0.06 mm for healthy women; p < 0.002)[12].

It is a matter of opinion whether the increase in BWT is a pathognomonic of BOO or not. Frequent involuntary contractions of detrusor muscle against the closed urethral sphincter complex are assumed to cause detrusor muscle hypertrophy and an increase in the BWT[9,15]. BWT was increased due to collagen and fibrous elements deposition due to the aging process. There was no significant difference in BWT between the unobstructed men of 60 years and those with BOO (3.57 ± 0.2 mm vs. 3.67 ± 0.11 mm, respectively)[12]. Blatt *et al.*[16] found no significant difference in the BWT patients with normal urodynamic investigations and those who were proven to have BOO or DO. They proved neither a significant gender difference, nor a statistical correlation between age and increase in BWT.

2.2. Detrusor wall thickness

Detrusor wall thickness (DWT) can be defined sonographically as the hypoechoic area between two hyper hypoechoic lines; the outer line represents the bladder adventitia and the inner line represents the bladder mucosa and submucosa[11,17]. The detrusor muscle is supposed to be the actual part of the bladder wall that shows increase in volume due to hypertrophy. Hypertrophy can be a result of contraction against high resistance due to either BOO[18] or detrusor overactivity (DO)[9]. Therefore, studies were performed to measure the mean DWT as an indicator of BOO in men with LUTS.

DWT decreases gradually with bladder filling up to 250 ml beyond which the DWT becomes stable with no further significant decrease. It demonstrates a significant difference between men and women (1.4 mm vs. 1.2 mm respectively; $p < 0.001$)[19]. This can be explained by the higher resistance met by the urine flow on passing the male prostatic urethra. Oelke *et al.*[18] suggested 2 mm as cut-off DWT for the diagnosis of BOO with 95.5% PPV. While Kessler *et al.*[20] reported 2.9 mm cut-off DWT to have a PPV of 100%, but with low sensitivity (43%).

Some of these studies showed good diagnostic accuracy in terms of likelihood ratio (LR) to detect BOO[21]. However, different devices were used, such as linear or convex scanning probes with different frequencies, depths of wave penetration, and zooming powers. This is probably the reason of inconsistence in results of their studies. All these factors make it difficult to compare all studies in a standardized analytic way, and strike a big query about reliability of measurement of BWT and/or DWT as a single diagnostic tool for BOO[22].

All these studies assume that the BWT is symmetrical all over the bladder. This may be inconsistent with the ultra-structural description of the bladder wall in men with BOO, which revealed a patchy distribution of the increased BWT[23].

This tool was proven to be a good predictor of BOO, but still cannot discriminate between different causes of infravesical obstruction such as BPH, bladder neck contracture, urethral stricture, or detrusor-sphincter dyssynergia. Moreover, it cannot differentiate between BOO or the frequently accompanying DO as the actual etiological reason for the increased DWT and/or BWT.

The procedure of measurement is simple, but still carries a potential bias of subjective error, especially with inexperienced observers. BWT and DWT were measured at different sides of the bladder wall, but not much attention was paid to the indentation effect of the nearby structures, such as bowel at the dome or pelvic organs at the bladder base. These factors may affect the accuracy and reproducibility of the measurement procedure. BWT and DWT decrease with increase in bladder filling. To overcome this problem, measurements were taken at fixed bladder volume, which hinders the clinical utility of this tool. The suggested BWTI needs to be applied in larger studies in children and also needs to be tested on adult population before it can be a broadly accepted solution of this problem in clinical practice.

2.3. Ultrasonic estimated bladder weight

One of the ultrasonic methods investigated as a non-invasive tool in the diagnosis of functional lower urinary tract disorders in both filling and voiding phases is ultrasonic estimation of bladder weight (UEBW). Kojima *et al.*[17] studied 10 bladder autopsies taken from 10 men between 25-92 years old. Bladders were filled with saline at fixed filling volumes and BWT was measured using ultrasound. The inner and outer bladder dimensions were also measured. The authors assumed the bladder to be as a sphere; the inner calculated bladder volume was subtracted from the outer total bladder volume. The outcome was multiplied by the specific gravity which equals approximately 1. Bladders were emptied and the actual weights were directly measured. Cross sections of the bladder wall were obtained and compared to ultrasonic measurements: the authors found no difference between the sonographic and the actual BWT. UEBW significantly correlated with the actual bladder weight ($r = 0.970$; $p < 0.0001$). However, it was smaller than the actual weight with a mean error of 12.5%.

One year later, Kojima *et al.*[24] applied this new tool as a diagnostic noninvasive method for BOO in 65 men with LUTS. Patients were classified as obstructed or unobstructed based on the conventional PFS diagnosis. UEBW was significantly higher in the obstructed group than in the unobstructed group (46.2 ± 13 g vs. 29.3 ± 9 g respectively; $p < 0.0001$). It correlated significantly with obstructive urodynamic parameters. The authors suggested UEBW to be a useful clinical tool in the diagnosis of BOO, especially for follow-up of patients who are subjected to medical treatment.

UEBW was suggested as a useful tool for follow-up in patients with BOO due to BPH after prostatectomy. UEBW significantly decreased from 52.9 ± 22.6 g to be 31.6 ± 15.8 g ($p < 0.0001$) in a series of 33 patients after 12 weeks follow-up post prostatectomy[25]. When investigated as a predictor for acute urinary retention in patients with LUTS, UEBW had a sensitivity and specificity of 74% and 71%, respectively using a cut-off value of 40 g[26]. UEBW offers a good solution for the bladder filling volume dependence problem, which may hinder the clinical utility of ultrasonic measurement of BWT and DWT. However, assuming the urinary bladder to be spherical in shape does not seem to match reality.

2.4. Ultrasonic estimated intravesical prostatic protrusion

The enlarged prostatic lobes can protrude through the urinary bladder neck causing mechanical obstruction during micturition[27]. The intravesical prostatic protrusion (IVPP) is defined sonographically as the distance between the top of the protruded prostate inside the bladder neck down to the end of the prostate base at bladder circumference. It was measured by trans-abdominal ultrasound (TAUS) in a study that included 200 men with LUTS[28]. IVPP was classified into three grades according to the degree of protrusion: grade I <5mm, grade II = 5-10 mm and grade III >10 mm. Patients were classified as obstructed or not using 'BOOI'. The IVPP grade had higher PPV for BOO than other parameters like Q_{max} or PVR (94% vs. 74% and 93% respectively). Grade III IVPP was associated with higher 'BOOI' than the lower grades ($p < 0.001$). The authors think that IVPP can be added to other established variables that are investigated routinely in a set of diagnosis of BOO.

Almost similar results were reported by studies done later. Lim *et al.*[29] studied 114 men with LUTS and BPH. They found IVPP to have the best correlation with BOO diagnosis defined by the 'BOOI' Remarkably, it was the only independent variable that was able to predict BOO ($p < 0.02$). Reis *et al.*[30] suggested an IVPP cut-off value of 5 mm for the diagnosis of BOO with sensitivity and specificity of 95% and 50%, respectively.

Like BWT and DWT, IVPP was proven to decrease with increasing bladder volume[31]. It means that IVPP should be measured at a certain filling volume, which may hinder the clinical utility of this tool. Also, it is useful only to exclude BPH as a single cause of BOO, which offers an anatomical but not functional diagnosis. If it is applied as a single diagnostic tool in patients suffering from BOO with BPH the functional status of the detrusor muscle will still be lacking. This fact lowers the diagnostic value of this tool, especially when a surgical intervention is an option in these patients. Most of the studies done to investigate IVPP did not include data about BWT and/or DWT. If these data were included, the diagnostic value of these studies would have been increased because of their expected relevant pathophysiology.

2.5. Ultrasonic measurement of post-void residual urine

PVR is defined as the amount of urine that remains in the bladder after completion of the act of micturition. It increases in patients with BOO[32]. A cut-off value of 100 ml was suggested as an indicator of poor voiding with a possibility of BOO[33]. However, for a long time, it has been a matter of opinion whether it is a reliable indicator for BOO or not. PVR was found to decrease in patients after surgical relief of their obstruction[34].

A large number of patients with clinically proven BOO have no significant PVR. Abrams *et al.*[35] found that in those patients with high PVR detrusor pressure at the end of the voiding the cycle is lower than expected. This implies that detrusor muscle contraction stops before completion of micturition. Therefore, it has been assumed that PVR increases as a direct result of bladder muscle decompensation due to long term BOO. PVR is thought not to be increased as a direct mechanical effect of urethral outflow obstruction, but it might reflect detrusor muscle underactivity rather than a true BOO. Kranse *et al.*[36] reported a weak correlation between BOO and PVR. They concluded that PVR still cannot be used as a single reliable diagnostic test for the diagnosis of BOO. Griffiths *et al.*[37] found that PVR increases with aging, even in the absence of obstruction. PVR shows large variations when measured in different day times in the same subject, with the largest amount being obtained in the early morning measurements. This means that PVR is influenced by the hormonal status and physical activities of the patient. If this could be controlled, PVR might be a reliable and reproducible clinical diagnostic tool for BOO[38].

Evaluation of PVR using ultrasonography is an easy and nice replacer for the conventional catheterization method, especially in relatively high risk patients, e.g. in patients with neurogenic bladder disorders and those with renal transplants. A large study included 324 men between 48-75 years old[39], where bladder diameters were obtained by sector ultrasound. After approximation to a geometric figure, the authors applied 11 formulas available in the literature at that time. The authors found the formula suggested by Org *et al.*[40] to have the greatest accuracy: *bladder volume = transverse depth X sagittal height X 12.56*. However, no single formula proved to be the best for quantitative assessment of PVR. The authors concluded that ultrasound can only replace the catheter when qualitative measurements are more important than quantitative ones, especially in risky patients.

All recent studies worked only on enhancing accuracy of ultrasonic estimation of PVR, but the major problem is still there: PVR cannot differentiate between BOO and detrusor underactivity. It is not reliable as a single diagnostic test of BOO, but can still be a useful tool in evaluating the treatment efficacy of various therapeutic modalities of BOO due to BPH.

2.6. Doppler ultrasound urinary flow velocity

Non-invasive Doppler ultrasound uroflowmetry (DUF) was introduced by Ozawa *et al.*[41] in 2 stages. The first stage was experimentally designed to test the sensitivity of DUF to detect flow velocity of fluids passed through an artificial urethral tube. This was based on a hypothesis that micro bubbles resulting from pressure fluctuation during fluid flow can cause the 'Doppler effect', which is a basic requirement to get a measurable Doppler flow.

In the second clinical stage, they developed a prototype robotic controlled Doppler probe holder applied to the perineum in two groups of patients. One of them was a control group, while the other group included patients with BOO. Combined measurements of DUF velocity (V) and flow rate (Q) were done using specially designed equipment for this purpose. The authors suggested a new variable, which is the functional cross sectional area of the urethra (A) to be a new reliable urodynamic parameter able to diagnose BOO. It is calculated from the equation: A (cm^2) = Q (ml/s) ÷V (cm/s). This parameter 'A' was significantly lower in the obstructed group than in the control group (0.31 ± 0.16 cm^2 vs. 0.73 ± 0.23 cm^2 respectively; $p < 0.006$)[41].

Two radiologically located anatomical sites were selected to measure the maximum DUFV. The first site is the distal prostatic urethra just above the external urethral sphincter where flow velocity one (V1) is measured. The second site is the membranous urethra where flow velocity two (V2) is measured. The result of dividing V1 by V2 is called the velocity ratio (VR). 'V' had a good correlation with 'BOOI' (r = 0.73; $p = 0.001$). All patients who had a 'VR' higher than 1.6 were classified as obstructed, while those with 'VR' lower than 1.1 were classified as unobstructed or equivocal, as compared to the conventional PFS diagnosis, having the 'AG' number respectively above or below 40[42].

DUFV measurement is non-invasive and offers both functional and anatomical diagnosis of BOO. However, it is still lacking data about detrusor contractility and is not a valid option in patients who cannot void. Moreover, it needs special equipment and software. More studies need to be done to evaluate its clinical applicability in the diagnosis of BOO.

2.7. Doppler ultrasonographic measurement of detrusor resistive index (RI)

Lin and Saito[43-44] showed in animal studies that the blood flow to the urinary bladder decreases in response to BOO. Based on this finding, trials to assess the arterial blood flow to the urinary bladder in patients with BOO were done. Naya *et al.*[45] applied color Doppler ultrasonography to evaluate the arterial blood flow to the bladder wall in 35 patients with increased UEBW. They determined the arterial resistive index (RI) as an indicator of blood flow changes: RI = $V_{max} – V_{min} / V_{max}$, where V_{max} and V_{min} are the maximum and minimum blood flow velocity respectively expressed in cm/s.

In patients with an increased UEBW measured at a fixed bladder volume of 100 ml, ’RI’ was able to distinguish BOO from neurogenic bladder wall hypertrophy as two major causes of abnormal increase in UEBW with 84% sensitivity, 76% specificity and 80% diagnostic accuracy for obstruction. Belenky *et al.*[46] reported 86% diagnostic accuracy of ’RI’ for BOO when measured in three different sites in the urinary bladder. The authors found no significant difference in Doppler readings with either empty or full bladders.

Applying the same technique using a transrectal approach to investigate the prostate gland in patients with clinical BOO and BPH, Kojima *et al.*[47] reported 85% sensitivity of prostate arterial 'RI' for BOO detection, but with low specificity of 46%.

These studies depend mainly on investigating the arterial hemodynamic changes in bladder wall or prostate gland that theoretically may develop in the course of the infravesical obstruction. This can be affected by some pathological conditions other than compensatory ischemic hypertrophy of the bladder wall, such as diabetic vasculopathy or atherosclerosis. None of these studies showed whether these factors were concerned or not, which makes the specificity of these methods questionable.

3. Perineal Noise Recording

Results of clinical vascular experiments done in the early seventies of the last century showed that carotid arterial stenosis of a patient with atherosclerosis has a characteristic turbulent flow distal to the site of obstruction. Investigators developed a so-called 'phono-angiogram' to detect this phenomenon[48]. Trials were expanded to urology in order to apply this audio technology to investigate urethral obstruction. An in-vitro study[49] was done to evaluate the phonographic characteristics of a silicon tube model of the male urethra through which a fluid passed under different grades of obstruction. The authors found that the mechanical vibrations induced by turbulent fluid in an obstructed urethral model could be measured using a microphone applied to the outer surface of the tube. The frequency spectrum of the vibration signals showed dependence on many factors; one of these factors was the degree of obstruction. In a clinical study that included 16 healthy volunteers[50], a microphone was pressed against the perineum just behind the scrotum and the acoustic signals during voiding were recorded. The authors reported significant, repeatable, intervolunteer differences in acoustic signal frequency with smaller intra-volunteer differences.

This method seems to be a potential non-invasive method for the diagnosis of BOO. But first it needs to be tested in patients with LUTS and clinical BPH in order to evaluate its clinical applicability compared to the standard PFS.

4. Non-invasive measurement of isovolumetric bladder pressure

Assuming that there is a continuous fluid column between the bladder cavity and the urethra during voiding, McRae *et al.*[51] proposed that the isovolumetric intravesical pressure can be measured indirectly by applying external compression with certain pressure, controlled by a manometer around the penile urethra.

Penile cuff method

Different methods were used applying the same principle; one of these methods was the penile cuff method. This method implied occluding the urine stream through the penile urethra by inflating a 2 cm wide penile cuff up to 250 cm H_2O. The patient was asked to start voiding once he felt urine passage down the urethra. Theoretically this means that pressure inside the distended part of the urethra proximal to occlusion is equal to the intravesical pressure. The high pressure inside the cuff was released slowly (8 cm H_2O/s) to allow voiding. Once a flow rate reading of 1 ml/s was reached, rapid deflation of the cuff was done. The cuff pressure at the first flow was suggested to be theoretically equal to the intravesical pressure. However, it was found to be higher than the actual intravesical bladder pressure measured by conventional PFS with a mean difference of 37±16 cm H_2O. A formula: [$R = P_{iso}/Qi^2$ (cm $H_2O/cc^2/s^2$)] was postulated to score obstruction in ascending grades from 1 to 3 points. This formula represents the energy transfer ratio between the maximum isovolumetric detrusor pressure (P_{iso}) and the maximum urethral carrying squared capacity (Qi^2). It was calculated in patients before and after they received a definitive treatment[52]. 'R' was remarkably improved in a patients' group that underwent surgical correction of their BOO. The average improvement was 62% for bladder neck incision procedures and 79% for transurethral prostatectomy (TURP) procedures. This improvement was less noticeable in patients who received conservative treatment.

These findings were obtained from a small number of 26 patients implying that statistical conclusions should be dealt with caution.

The penile cuff inflation method was tried to increase the accuracy of the isovolumetric bladder pressure measurement. A cohort of 35 patients was included in a clinical study[53] in which an automatically inflatable penile cuff was applied around the penile urethra. Once voiding started gradual increase in pressure at a rate of 10 cm H_2O per second was done until voiding stopped. Intra-urethral pressure was found to be affected significantly by the penile size (p = 0.002) and the material of the cuff (p = 0.001). The authors recommended the use of cuffs with a width of 40 to 50 mm and soft pliable materials to get optimal results.

A larger study was performed on 151 men with LUTS[54] who underwent non-invasive measurement of isovolumetric bladder pressure using the penile cuff inflation test with simultaneous conventional PFS. The cuff derived mean intra-urethral pressure was higher than the actual mean intravesical pressure derived from PFS by 16 cm H_2O. This can be explained by the lower position of the penile cuff than the actual intra-pelvic position of the bladder. Interestingly, the patients completed a questionnaire where 80% of them preferred the use of penile cuff test instead of the conventional PFS.

A nomogram was developed by plotting the isovolumetric bladder pressure values obtained from the penile cuff test against the Q_{max} values obtained from conventional uroflowmetry done in the same patients in a clinical study that included 144 patients with LUTS[55]. At Q_{max} <10 ml/s it was possible to classify these patients into obstructed, unobstructed and equivocal groups with sensitivity, specificity, PPV, and NPV of 59%, 89%, 77% and 77%, respectively for obstruction. The nomogram could identify good symptomatic outcome with 50% improvement of the IPSS four months after surgery in a study performed on 208 patients planned for TURP[56] with predictive values of 87% and 56% in respectively obstructed and unobstructed patient groups. It was remarkable that only 2% of the patients reported a self-limited urethral bleeding and pain as adverse events.

Condom catheter method

An external, self adhesive, condom catheter has been introduced for the first time by Ron van Mastrigt *et al.* for the non-invasive measurement of the isovolumetric pressure[57,58]. The rationale behind this the technique was that intravesical pressure could be measured in the periphery (urethra) non-invasively, rather than inside the bladder through an invasive catheter, having a continuous column of fluid between the inside of the bladder and the urethra.

Forty-six patients with LUTS underwent invasive pressure flow study with simultaneous measurement of isovolumetric pressure using the condom catheter technique. The condom catheter used in this technique consisted of 4 basic components: a condom that fits to the penis, a tube that drains in a flowmeter, a valve and a pressure transducer. During voiding, the urine outflow is interrupted by closing the tube with the valve. The pressure transducer measures the pressure inside the condom at that moment and displays a flow rate on a computer screen.

In 26 successful measurements, the agreement between the pressure inside the bladder (invasive) and outside the bladder (condom) was better in the patients with no obstruction than in the group of obstructed patients. The pressure inside and outside the bladder was significantly different between both groups. The pressure difference between the pressure inside and outside the bladder showed significant correlation with the urethral resistance factor (URA)[58].

A nomogram was further constructed based on condom pressure values plotted versus flow rate values. About 92% of patients were successfully reclassified as having BOO or not compared to a conventional pressure flow study[59].

The applicability and reproducibility of the non-invasive condom catheter method was addressed in 730 volunteer men who were able to void continuously with a Q_{max} of at least 5.4 ml/s to ensure accurate reflection of the bladder pressure[60]. A modified condom type catheter was used. The condom had a stiff shaft to withstand high pressures and it was connected to 3 tubes that could be controlled separately by pneumatic valves. The tubes had connections to a dome that is screwed on a pressure transducer and provided with three different metal outflow resistances. Once the patient starts voiding, the outflow resistance was gradually increased through controlling different tubes until the flow was completely interrupted; theoretically, at this point, condom pressure reflected the isovolumetric pressure inside the bladder.

A total of 659 were eligible for inclusion in the condom measurements; 618 patients had at least one successful measurement and were therefore included in the final analysis. The mean maximum pressure measured by the condom type catheter was 101±34 cm H_2O. A total of 555 patients underwent two successful measurements in the same session on the same day. In 80% of them, the mean difference between the two pressure values recorded by condom catheter was -1 cm H2O, significantly different from 0 (p<0.001). About 10% of the patients reported a short term, tolerable unpleasant sensation on the glans penis during the test and 7% reported self limiting terminal hematuria.

Indirect measurement of isovolumetric bladder pressure is an easy technique with an acceptable low morbidity. The rational of this method sounds logic, because it implies measurement of a urodynamically important and widely acceptable parameter. This is lacking in all other non-invasive urodynamic methods. Therefore, this technique has similarities with the conventional PFS and can be potentially informative in case of detrusor under activity. However, it cannot prove or exclude the effect of changes in the abdominal pressure on the vesical pressure.

5. Quantitative near-infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is an optical technology. Light in the near-infrared spectrum can penetrate the skin to underlying tissues to be absorbed by naturally occurring chromophores. Examples of these chromophores are oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (HHb). O_2Hb and HHb absorb light photons in the near-infrared spectrum at different wavelengths. Therefore, measurement of changes in their concentrations in biologic tissues at a certain moment relative to baseline can give an idea about the relevant oxygen dependant hemodynamic changes in these tissues at that moment[61,62]. Recently, the feasibility of urinary bladder monitoring with NIRS has been proven by Macnab *et al.*[63].

Stothers *et al.*[64] evaluated 64 men with LUTS using conventional PFS with simultaneous NIRS of the bladder. Patients were classified into obstructed and unobstructed groups based on ’Abrams-Griffiths nomograms’. A classification and regression tree (CART) model was applied to determine the independent ability of NIRS data to reclassify patients as compared to the standard PFS. The authors reported a good discriminatory ability of NIRS data related to obstruction with 100% sensitivity and 88% specificity for BOO.

The chronicity, degree of obstruction, systemic vasculopathies and the potential effect of BWT should be considered when NIRS is applied as a single tool of investigation in voiding dysfunctions[65].

Non-Invasive Techniques in the Diagnosis of Voiding Disorders

The techniques developed for the non-invasive diagnosis of BOO in men with voiding LUTS were based on two approaches. The first approach was indirect measurement of the isovolumetric bladder pressure during voiding, which is a crucial urodynamic parameter. This technique demonstrated good accuracy as compared to the conventional PFS. Accordingly, PFS are not any more unique in their ability to identify intravesical pressure. However, more attention should be paid to the abdominal pressure contribution and its impact on the results in this technique. The second approach was measurement of theoretically relevant, non-urodynamic parameters to BOO such as BWT, DWT and UEWB. These sonographically derived parameters showed good correlation to BOO, but are still lacking standardization of methodologies followed in their measurements. Cut-off values of these parameters need to be developed for patients in various ages and genders in order to be reproducible in clinical practice. DUF, perineal sound, NIRS, and Doppler RI show growing evidence, but their reproducibility still needs to be tested in larger patient study groups to determine their clinical utility.

We think that if NIRS, DUFV or IVPP techniques are combined with other non-invasive parameters such as IPSS, Q_{max}, prostatic volume, PVR, BWT, DWT and UEBW more effective and clinically expressive diagnostic performance of these parameters will be obtained.

Flowmetry and ultrasonographic assessment of PVR cannot distinguish BOO from detrusor undercontractility but can still be applied for initial evaluation and follow-up of patients with LUTS. NIRS detects the hemodynamic changes caused by detrusor contractions. More basic and clinical studies are needed to evaluate the value of this technology in the non-invasive diagnosis of BOO.

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CHAPTER 5

Applicability of a Disposable Home Urinary Flow Measuring Device as a Diagnostic Tool in the Management of Males with LUTS

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Abstract

Introduction

To investigate the accuracy of uroflowmetry with disposable Q_{Single} compared to measurements with home-based digital device and compared to a single clinical measurement.

Patients and Methods

60 men with LUTS were included in a prospective, open-label, multicentre study. Uroflowmetry measurements were done using three devices/methods: single clinic-based method, followed by up to 12 measurements using the disposable home-based Q_{Single}, and up to 12 measurements using a home-based digital device. Subjective data on ease of use of Q_{Single} and preference of patients were investigated and objective measures of Q_{max} and voided volume from the three devices were compared.

Results

Mean Q_{max} values of 12, 13 and 16 ml/s were achieved with Q_{Single} device, standard clinic method, and digital device, respectively. Mean Q_{max} obtained with Q_{Single} device did not differ from the one obtained with clinic method. A significantly higher mean Q_{max} was recorded for the digital device. Mean voided volumes recorded with each device differed marginally. Handling capabilities of the Q_{Single} device were considered good by all subjects.

Conclusions

The accuracy of Q_{max} and voided volume mean measurements with Q_{Single} was comparable to one standard clinic recording. Q_{Single} offers a viable alternative to reduce the number of clinic visits and can be used by other care givers.

Introduction

Clinical uroflowmetry has been recommended to be performed before surgical intervention for male patients with lower urinary tract symptoms (LUTS) suggestive of bladder outlet obstruction (BOO) in order to exclude patients unlikely to benefit from the surgery[1]. It can also be of great value in the evaluation of treatment outcomes in these patients. However, clinic-based uroflowmetry has some flaws: the setting is artificial and often it is difficult to void at the desired moment. Moreover, a single measurement of the voided Q_{max} is a poor representative for the ‘best value’ to objectively characterize patients’ voiding parameters since there is a high variability of Q_{max}[2]. On the other hand, performing multiple uroflowmetries necessitates multiple visits to the hospital with increased costs.

Therefore, there is a need for representative and accurate way of recording uroflowmetry parameters that is more patient friendly. This study investigated whether repeated measurements using a single use uroflowmetry device, Q_{Single}, would result in a repeatable and accurate measurement of uroflowmetry parameters compared to a single clinic-based measurement.

Patients and Methods

Participants:

Sixty-eight male subjects with LUTS suggestive of BOO were screened for the study. Subjects were ineligible if they were practicing clean intermittent self-catheterization (CIC), had an ongoing symptomatic urinary tract infection (UTI), suffered from neurogenic bladder, had started treatment with BPH medication within the last 2 months, or had presented with signs of severe urinary flow obstruction.

Study Design:

This was a prospective, open-label, multicentre investigation. All subjects underwent serial measurements of their maximum urinary flow rate (Q_{max}) and voided volumes in three different settings: the first by doing a single measurement using the standard clinical uroflowmeter (Q_{clinic}) (supplied by Dantec, Medtronic or Urocap). This was followed by performing up to 12 measurements using Q_{Single} (AstraTech AB, Sweden) home-based uroflowmeter (Q_{Single}). Finally, up to 12 measurements were done using Urospec™ (Medispec), a home-based digital uroflowmeter ($Q_{digital}$). The order of the two types of home-flow measurements was determined at random. Measurements obtained by the digital device were used as the reference standard in our study.

Figure 1. Q_{Single} device

Home-flowmetry Devices:

Q_{Single} (AstraTech AB, Sweden) is a single-use disposable device to measure Q_{max} and total voided volume. The device (*figure 1*) has been developed to offer a simple uroflowmetry measurement at home. The product displays the results in a stepwise manner and the results are transferred to a removable scratch card. On the device there are indicators showing stepwise increments in Q_{max} from 0 to 17 ml/s. It also contains a reservoir with a printed scale to house the voided volume in interval steps ranging from 50 to 600 ml. Urospec™ digital uroflowmeter (Medispec) is a battery operated unit that provides measurement of Q_{max}, voided volume, weight, voiding time and voiding frequency. Data are stored in an internal memory. The Urospec™ flowmeter was the reference to which the other devices were compared.

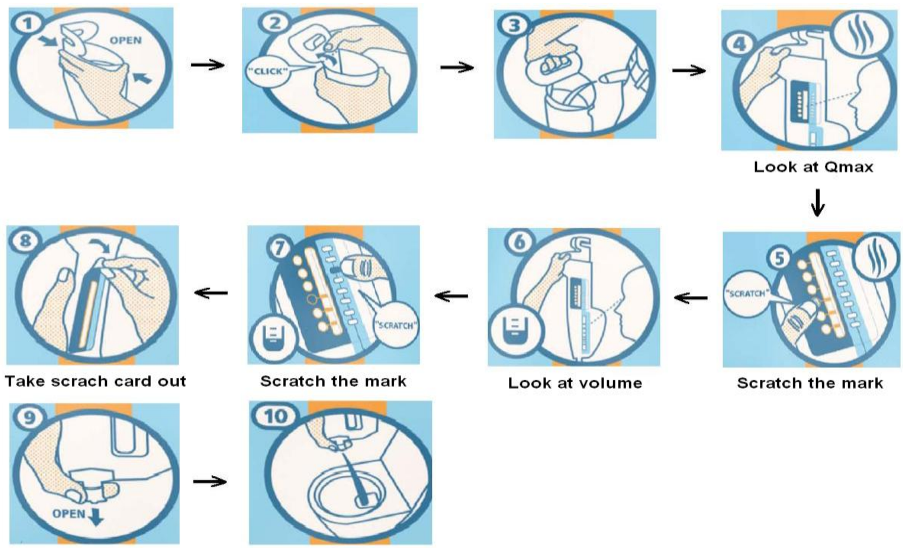

Figure. 2. Instructions for the patient showing steps to use the Q_{Single} device.

Investigative studies:

All subjects were instructed to record up to 12 consecutive representative urinary voids using the Q_{Single} and then using $Q_{digital}$ device at home. Instructions for patients on how to use the Q_{Single} are illustrated in *figure 2*. After the home recording sessions, patients returned the $Q_{digital}$ device together with a voiding diary from Q_{Single}. Patient also completed a questionnaire about their experiences with the various devices. The questionnaire included a number of questions related to the perception of use and handling of the respective measuring devices. For the new Q_{Single} device, a number of questions related to handling capabilities were included.

Ethics:

The study was performed in accordance with the Declaration of Helsinki and it was consistent with ISO 14155 and ICH/Good Clinical Practice and applicable regulatory requirements. The study was approved by the Ethics Committee/Institutional Review Board in each participating centre.

Statistical Analysis:

The primary objective was to determine the diagnostic accuracy of the Q_{max} obtained from at least 3 to a maximum of 12 measurements using the Q_{Single} device compared to the accuracy of the Q_{max} obtained from the single measurement using Q_{clinic}. Three measurements with the Q_{Single} device were taken because this was considered an adequate number to be reliable. The outcome was related to the mean Q_{max} obtained from the 12 measurements performed using the $Q_{digital}$.

Secondary study objectives were to evaluate results for different subgroups of subjects. The study was analyzed applying the principles Intention-to-treat (ITT) and per-protocol (PP). The ITT-analysis was considered the primary analysis set. Subjects fulfilling the eligibility criteria and presenting with evaluable data were included in the PP analysis set.

The size of the trial was calculated based on estimations from technical specifications from each device and data from the literature of mean Q_{max} to be expected in this study population[3]. The study was designed with an 80% power to detect a difference in flow of >2 ml/s at a significance level of 5%. The aim was to include 75 subjects. Based on an interim analysis, a total of 60 subjects were deemed sufficient for statistical comparison.

From the individual data collected, differences in mean values of voided volumes and Q_{max} were calculated for each subject and tested using the Wilcoxon signed-rank test. Similarly, individual differences were calculated between measurements from the three devices.

Each Q_{max} collected was put into eight categories in accordance with the scale available on the Q_{Single} (*table 1*). Individual paired mean Q_{max} values for each subject and method/device were categorized according to the scale. No covariates were judged to influence the outcome of the variables. Recorded urinary flows below the requested amount of 100 ml were excluded from analysis[4].

Table 1. Categories for comparisons of individual mean Q_{max} for each device/method

Category label	Q_{max} interval for each category label
0	0
5	$0 < Q_{max} < 6$
7	$6 \leq Q_{max} < 8$
9	$8 \leq Q_{max} < 10$
11	$10 \leq Q_{max} < 12$
13	$12 \leq Q_{max} < 14$
15	$14 \leq Q_{max} < 16$
17	$16 \leq Q_{max} < \infty$

Results

Sixty-eight men with LUTS suggestive of BOO were screened for the study; of these a total of 60 subjects with a mean IPSS of 17.4 (range 2-38), a mean age of 66 years (range 43-84) and a mean period with LUTS of 5.8 years (range 0-38) were recruited. As there were some missing data in various registrations for 8 patients, study data were also analyzed according to the principles of a PP analysis to check the robustness of the ITT analysis. This analysis did not show any important differences and is therefore omitted from presentation.

One more patient was excluded due to data loss. The results of the three different methods obtained from a total of 59 subjects using Q_{clinic}, Q_{Single}, and $Q_{digital}$ are shown in *table 2* and *figure 3*. The mean urinary volumes recorded with each device were 250, 238 and 224 ml for Q_{clinic}, Q_{Single}, and $Q_{digital}$, respectively. This was not statistically different. Mean Q_{max}-values of 12, 13 and 16 ml/s were recorded with Q_{Single}, Q_{clinic}, and $Q_{digital}$, respectively.

For Q_{Single}, the mean Q_{max} from the first three consecutive measurements was very similar to the data from the total of 12measurements. For $Q_{digital}$, a significantly higher mean Q_{max} was recorded.

Q_{single} vs. Q_{clinic}

Computed individual mean values from each subject's measurements of Q_{max} values and voided volumes were used to compare the Q_{clinic} and the Q_{Single} device. Q_{max} recorded by Q_{clinic} was not significantly higher than Q_{max} recorded by the Q_{Single} device (*table 3*). The same was true for the mean voided volumes per void.

Table 2. Flow measurements with the Q_{clinic}, Q_{Single}, and the $Q_{digital}$ devices

	n	Mean	SD	Min	Max
Q_{clinic} [a, b]					
Q_{max} ml/s	59	13	7	5	39
Voided volume, ml	59	250	130	30	566
Q_{Single} [c]					
Q_{max}, ml/s, all	57	12	4	4	17[d]
Q_{max}, ml/s, first 3 assessments	57	12	4	3	17[d]
Voided volume, ml, all	57	238	94	79	508
Voided volume, ml, first 3 assessments	57	234	104	67	533
$Q_{digital}$ [e]					
Q_{max}, ml/s	52	16	8	6	47
Voided volume, ml	52	224	76	85	457

[a] Equipments from Dantec Dynamics Ltd, Medtronic Inc. or Laborie Medical Technologies Inc. [b] Three subjects had 2 Q_{clinic} measurements. [c] Data from 57 subjects (2 subjects reported 9 measurements). [d] Maximum value of registration, flows exceeding 17 ml/s are also registered as 17 ml/s. [e] No data from 8 subjects (3 subjects reported 9-11 measurements)

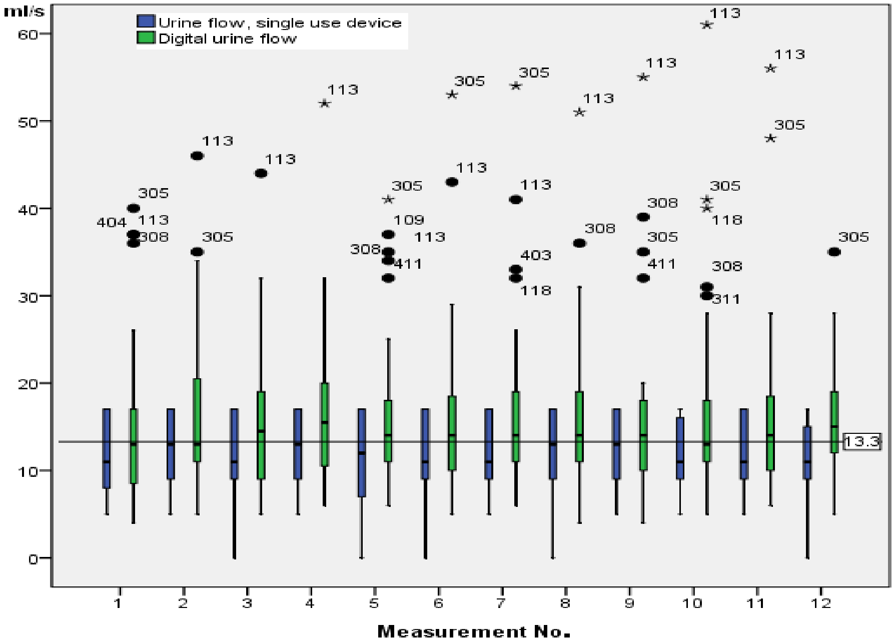

Figure 3. Q_{max} for measurements 1-12 with Q_{Single} and $Q_{digital}$ device. The Q_{clinic} average flow of 13.3 ml/s is marked as a reference line.

$Q_{digital}$ vs. Q_{clinic} and $Q_{digital}$ vs. Q_{Single}

Individual mean voided volumes and Q_{max} were also used for calculation of the differences between $Q_{digital}$ and Q_{clinic} and for the differences between $Q_{digital}$ and Q_{Single} devices, respectively. The lowest mean voided volume was obtained with $Q_{digital}$ and the highest value with Q_{clinic}. No statistically significant differences were obtained regarding voided volumes. The Q_{max} with the $Q_{digital}$ device was 3 ml higher than with the Q_{clinic} (p = 0.0001) and 4 ml higher than with the Q_{Single} device (p< 0.0001).

Comparisons of paired Q_{max} values

Individual categorized paired Q_{max} values are presented in *tables 3, 5 and 7*. Twenty-three subjects had a higher Q_{Single}-Q_{max}, whereas 23 subjects had a higher Q_{clinic}-Q_{max} (p = 1.0). $Q_{digital}$-Q_{max} was higher in 26 subjects; 8 subjects had a higher Q_{clinic}-Q_{max} (p = 0.0029).

Table 3. Paired categorized mean Q_{max} flow rates (ml/s) for the Q_{clinic} and the Q_{Single} device.

Device used		Q_{Single} mean of 3 measurements								
		0-5	5-7	7-9	9-11	11-13	13-15	15-17	17-	Total
Q_{clinic}	0-5									0
	5-7						1			1
	7-9		2	2	3		1			8
	9-11		1	3	2			2	1	9
	11-13		1	2	1	2	2			8
	13-15		1		1	2		4	2	10
	15-17					4	1	1	7	13
	17-						3	1	3	7
	Total	0	5	7	7	8	8	8	13	56

Number of subjects (n) in each interval. Green boxes denote equivalence.

Table 4. Paired categorized mean Q_{max} flow rates (ml/s) as ≤10.0, 10.1-15.0 and ≥ 15.0 for the Q_{clinic} and the Q_{Single} device.

Device used		Q_{Single} mean of 3 measurements			
		0 - 10	10 - 15	15 -	Total
Q_{clinic}	0 - 10	14	4	1	19
	10 - 15	5	11	8	24
	15 -	0	7	6	13
	Total	19	22	15	56

Number of subjects (n) in each flow interval. Green boxes denote equivalence.

Finally, 33 subjects had a higher $Q_{digital}$-Q_{max} compared to 5 subjects with a higher Q_{Single}-Q_{max} (p < 0.0001). Paired Q_{max} values were re-categorized based on the Q_{clinic} data into three groups <10, 11-15 and >15ml/s to analyze how many patients switched these categories based on the home-based flowmetry data (*tables 4, 6, 8*). Interestingly, 81% of the subjects preferred to measure their urinary flow at home. The handling capabilities of the Q_{Single} device were well appreciated by all subjects.

Table 5. Paired categorized mean Q_{max} flow rates (ml/s) for the Q_{clinic} and the $Q_{digital}$ device.

Device used		$Q_{digital}$								
		0-5	5-7	7-9	9-11	11-13	13-15	15-17	17-	Total
Q_{clinic}	0-5									0
	5-7								1	1
	7-9			1	1	3	2	1		8
	9-11				2	3		2	1	8
	11-13			1	2	2		3		8
	13-15						2		5	7
	15-17						2	6	4	12
	17-							3	4	7
	Total	0	0	2	5	8	6	15	15	51

Number of subjects (n) in each flow interval. Green boxes denote equivalence.

Table 6. Paired categorized mean Q_{max} flow rates (ml/s) as ≤10.0, 10.1-15.0 and ≥ 15.0for the Q_{clinic} and the $Q_{digital}$ device.

Device used		$Q_{digital}$			
		0 - 10	10 - 15	15 -	Total
Q_{clinic}	0-10	6	9	3	18
	10-15	3	6	11	20
	15 -	0	4	9	13
	Total	9	19	23	51

Number of subjects (n) in each flow interval. Green boxes denote equivalence.

Table 7. Paired categorized mean Q_{max} flow rates (ml/s) for the Q_{Single} and the $Q_{digital}$ device.

Device used		$Q_{digital}$								
		0-5	5-7	7-9	9-11	11-13	13-15	15-17	17-	Total
Q_{Single}	0-5									0
	5-7			2			2			4
	7-9				4	3				7
	9-11				1	3	2	1		7
	11-13					1	1	3	1	6
	13-15						1	5	2	8
	15-17						1	3	4	8
	17-					1		3	8	12
	Total	0	0	2	5	8	7	15	15	52

Number of subjects (n) in each flow interval. Green boxes denote equivalence.

Table 8. Paired categorized mean Q_{max} flow rates (ml/s) as ≤10.0, 10.1-15.0 and ≥ 15.0 for the Q_{Single} and the $Q_{digital}$ device.

Device used		$Q_{digital}$			
		0 - 10	10 - 15	15 -	Total
Q_{Single}	0-10	9	8	1	18
	10-15	0	10	10	20
	15 -	0	2	12	14
	Total	9	20	23	52

Number of subjects (n) in each flow interval. Green boxes denote equivalence.

Discussion

'The bladder is an unreliable witness'[5]. This widely accepted dogma led to the development of a range of alternative investigations to supplement the patient's subjective assessment of LUTS. Pressure flow study (PFS) is the current standard urodynamic test for the diagnosis of male LUTS. However, it is invasive and can cause patient discomfort. Uroflowmetry is a non-invasive test and it has been widely used as a screening tool for men presenting with LUTS. Uroflowmetry is superior to reliance on symptoms alone[6-9]. It is valuable to quantify impaired urinary flow and can be used for follow-up after treatment[9], which can reduce the number of unnecessary, invasive pressure flow study.

The combination of uroflowmetry with post void residual measurement can be of value in male LUTS assessment as expressed in various European guidelines[10-12]. However, it was recommended by the National Institute for Health and Clinical Excellence (NICE) only as secondary assessment tool in these patients as they did not sufficiently increase the accuracy of BOO diagnosis and therefore could not be considered as cost-effective primary diagnostics[13].

A recognized problem with clinical uroflowmetry is that it may not be representative of what is normal for the individual; the circumstances in which the clinical uroflowmetry are measured are not totally physiological as patients have to present to the clinic holding their urine, and often they have to visit the toilet earlier than planned for uroflowmetry. Moreover, not every health care professional interested in voiding has a uroflowmeter and ultrasound equipment. Many general practitioners and neurologists seeing patients with voiding complaints would like to have an impression about patients' voiding capabilities[14,15]. Symptoms, voiding diaries, uroflowmetry and postvoid residual in combination could provide a potential prediction of obstruction in many cases, which may reduce the further need for invasive testing. This implies that a good alternative device for clinical uroflowmetry could be valuable for many healthcare professionals.

Home-based uroflowmetry could be such an alternative; various types of home-based uroflowmetry devices are available[16,17]. However, most of them are not disposable and are therefore costly[17,18]. Q_{Single} was developed based on an idea by Pel *et al.*[19]; the flowmeter consists of a funnel connected to a collecting tube. Urine coming into the funnel is collected and exits through one or more ports. The higher the flow rate; the more exit ports emit the urine.

This study aimed to evaluate the applicability and accuracy of home-based uroflowmetry measurement using a single-use flowmetry device compared to the standard method of clinic-based uroflowmetry. The average of the first three home-based uroflowmetry measurements was almost identical to all available measurements (*table 2*). Thus, three uroflowmetry

measurements using Q_{Single} seem to give a representative estimate of a patient's urinary flow comparable to clinic-based uroflowmetry.
The Q_{max} and voided volumes obtained with Q_{Single} were slightly lower than the ones obtained from one clinic-based flow measurement; this implies that Q_{Single} is a reliable device with the potential to replace clinic-based flows, and that the Q_{Single} does not under- or overestimate the voiding capabilities of patients.

A limitation of our study was that we used only one clinical flow as a reference although we know that only one flow is not as representative as the mean of several flow measurements. However, we used this design because we know that in clinical practice decisions are often made on the basis of a single clinic-based measurement. Another limitation was that Q_{Single} can only measure Q_{max} up to 17 ml/s. Moreover, a substantial proportion of patients did not suffer from severe LUTS.
The subjects in this study preferred home-based uroflowmetry over clinic-based uroflowmetry; similar observations have been made in previous studies[16,20]. Home-based uroflowmetry using the Q_{Single} device seems to offer a simple, convenient alternative to clinical-based uroflowmetry.

Data from this study suggest that the Q_{Single} device can be used in a urological practice as a reliable home-based method where patients can do measurements in their own environment with the potential to reduce the number of clinic visits.

Conclusions

Measurements with the Q_{Single} device compared to the standard clinic-based method resulted in similar voided volumes and Q_{max}-values. The disposable single-use device was considered easy to manage and was preferred by the majority of subjects. The Q_{Single} device may be useful as an inexpensive tool for monitoring LUTS in a non-urological healthcare setting.

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CHAPTER 6

Near-Infrared Spectroscopy of the Urinary Bladder During Voiding in Men with Lower Urinary Tract Symptoms: a Preliminary Study

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Submitted

Abstract

Introduction

To determine the difference in response of near-infrared spectroscopy (NIRS) of the bladder during voiding between men with and without bladder outlet obstruction (BOO) and also to determine the diagnostic value of NIRS in men with lower urinary tract symptoms (LUTS).

Methods

A prospective case series study included men with LUTS. Patients completed an International Prostate Symptom Score (IPSS) questionnaire and prostate volumes were measured sonographically**.** Patients underwent pressure flow study (PFS) with simultaneous NIRS of the bladder. Amplitudes of deoxy-hemoglobin (HHb), oxy-hemoglobin (O_2Hb) and total hemoglobin (Hb_{sum}) were calculated at Q_{max}, relative to baseline**.** Patients were urodynamically classified as obstructed or unobstructed. A recursive partition analysis (RPA) was performed to reclassify patients using NIRS amplitudes, followed by combined data of NIRS amplitudes, prostate volume, IPSS and Q_{max} to determine the best predictor(s) of BOO.

Results

Thirty-six patients were included. PFS classified 28 patients as obstructed and 8 as unobstructed. The median HHb and Hb_{sum} amplitudes were significantly higher in the obstructed group**.** RPA of NIRS relative amplitudes correctly reclassified 89% of patients [AUC: 0.91]. RPA of the combined IPSS, prostate volume, PVR and Q_{max} correctly reclassified 72% of patients [AUC: 0.84]**.** When NIRS amplitudes were added to this combination, RPA revealed a significantly (P<0.001) higher rate of correct reclassification in 89% of patients with 89.3% sensitivity and 88% specificity for obstruction [AUC: 0.96].

Conclusions

NIRS data can be of diagnostic value for BOO in men with LUTS either alone, or in combination with other non-invasive parameters.

Introduction

Benign prostatic hyperplasia (BPH) is a common disease in elderly men. BPH can be a leading cause of bladder outlet obstruction (BOO) and lower urinary tract symptoms (LUTS). Twenty-five percent of men above 60 years require surgical treatment for BOO[1]. BOO is characterized by an increase in detrusor pressure with a decreased urinary flow rate during voiding[2]. A pressure flow study (PFS) is the current standard diagnostic test for BOO[3]. However, this test is invasive with potential morbidity. Therefore, it is worthwhile to develop a non-invasive diagnostic technique for BOO.

Doppler ultrasonographic studies and radioisotope labeled microsphere techniques have revealed significant hemodynamic changes in the urinary bladder during the micturition cycle. Near-infrared spectroscopy (NIRS) is a function imaging technology. It enables non-invasive evaluation of oxygen dependent hemodynamic changes in biological tissues by measurement of the relevant changes in the concentration of tissue hemoglobin. Oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (HHb) represent both oxygen supply and consumption of the tissue. The sum of O_2Hb and HHb (Hb_{sum}) represents the total blood perfusion of the tissue under monitoring[4-6].

Macnab *et al*. applied qualitative NIRS patterns combined with maximum flow rate (Q_{max}) and post-void residue (PVR) in classification of men with LUTS[7]. Stothers *et al*.[8] evaluated 64 men with LUTS using conventional PFS with simultaneous NIRS of the bladder during voiding. Authors reported a good discriminatory ability of NIRS data related to obstruction with 100% sensitivity and 88% specificity for BOO.

In the current study, a quantitative approach of NIRS parameters was used. Our objective was to determine the difference in the response of NIRS data from the bladder during voiding between men with and without BOO. A secondary objective was to determine the diagnostic value of NIRS in men with LUTS suggestive of BOO, either alone, or in combination with other non-invasive diagnostic parameters of prostate volume, International Prostate Symptom Score (IPSS) and Q_{max}.

Patients and Methods

Participants were adult men referred to the Radboud University Nijmegen Medical Centre for urodynamic evaluation of their LUTS. Exclusion criteria were hematuria, a scar of previous pelvic surgery and a history of radical prostatectomy. The protocol for this study has been approved by the local Ethics Committee of the Radboud University Nijmegen Medical Centre (2009/188) and conforms to the provisions of the Declaration of Helsinki.

Patients received no medication for their urologic disorders prior to the date of investigation. Patients completed the IPSS questionnaire. Transrectal ultrasound was performed to measure the prostate volume. Dipstick urinalysis was performed to exclude hematuria and urinary tract infection.

All patients underwent PFS (Solar, Medical Measurement Systems, Enschede, The Netherlands). A gas filled urethral catheter (6 Fr/Ch) and a rectal catheter were inserted to monitor vesical pressure (P_{ves}) and abdominal pressure (P_{abd}), respectively. Water was infused at room temperature at a rate of 50 ml/min until maximum capacity was reached. Then, the patients were asked to void in the flowmeter in sitting or standing position according to their preference. Simultaneous trans-cutaneous NIRS of the bladder was performed during the PFS (URO-NIRS™, Urodynamix

Technologies Ltd, Vancouver, BC, Canada). NIRS optodes were placed on the abdomen 2 cm above the pubic symphysis across the midline[9]. Patients were asked to remain still in standing or sitting position to have baseline readings of the NIRS curves. Then, permission to void was given and patients were asked to avoid straining. Simultaneous PFS and NIRS data acquisition was performed with a sampling frequency of 10 Hz.

Data pre-processing and analysis

Data processing was performed by using MATLAB software (MATLAB R2009a, version 7.8.0.374, The Mathworks Inc, Natick, Massachusetts, USA). NIRS data was filtered using a second order Butterworth low-pass filter with a cut-off frequency of 0.2 Hz.

Two points were marked on the detrusor pressure (P_{det}) curve during voiding activity (*figure 1*); point 'A', at the beginning of detrusor muscle contraction and point 'B' at $P_{det.Qmax}$. Baseline readings of HHb, O_2Hb and Hb_{sum} curves were obtained by averaging 30 seconds of data before point 'A'. Relative amplitudes of NIRS curves were calculated by subtracting the averaged 30 seconds baseline of every curve from the point 'B' of the same curve.

Patients were urodynamically classified as obstructed or unobstructed using 'Detrusor/flow plot' according to Griffiths[10]. Diagnosis of obstruction was made when the group-specific resistance factor (URA) was >28. To obtain an 80% probability of detecting a difference of 3 µmol/l in NIRS amplitudes between the obstructed and the unobstructed groups, a 2-tailed alpha level was set at $\alpha = 0.05$ and a standard deviation of 3; the sample size needed was found to be 33 patients.

Median (range) demographic, urodynamic and NIRS parameters were calculated. A Mann Whitney U-test was applied to test the differences between groups. Differences with p-values less than 0.05 were considered statistically significant.

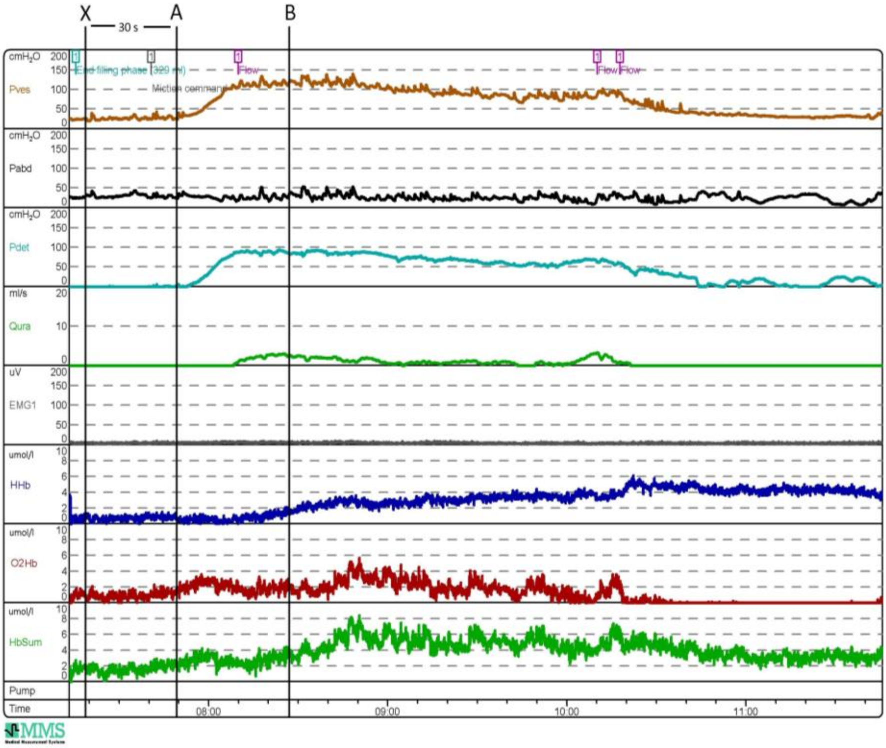

Figure 1. An example of voiding session without potential motion artifacts. Pressure flow study with simultaneous near-infrared spectroscopy (NIRS) of a man with LUTS bladder outlet obstruction. Thirty seconds of baseline were averaged between points 'X' and 'A' for all NIRS parameters. The amplitudes of change in deoxy-hemoglobin (HHb), oxy-hemoglobin (O_2Hb), and total hemoglobin (Hb_{sum}) were calculated as out the result of subtracting the averaged 30 s baseline form the values at point 'B' for each NIRS parameter.
P_{ves} = vesical pressure, P_{abd} = abdominal pressure, P_{det} = detrusor pressure, Qura = urinary flow rate. FS = first sensation, SD = strong desire, MCC = maximum cystometric capacity.

Statistics

Recursive partition analysis (RPA)[11] was then performed to test the ability of NIRS relative amplitudes to predict obstruction. RPA is a non-parametric method that recursively partitions data for relating independent variable(s) (NIRS and other non-invasive parameters) to a dependent variable (urodynamic diagnosis) creating a tree of partitions. It finds a set of cuts of the independent variable(s) that best predict the dependent variable by searching all possible cuts until the desired fit is reached. RPA was performed to test the ability of the combined data of prostate volume, IPSS and Q_{max} to predict obstruction. Finally, RPA of the combined data of NIRS amplitudes, Q_{max}, IPSS and prostate volume was performed to explore the clinical usefulness of quantitative NIRS when combined with these parameters in the diagnosis of BOO in men with LUTS.

The sensitivity and specificity in predicting obstruction together with the area under the receiver-operating curve (AUC) were calculated. An AUC of 1 indicates a perfect test in predicting obstruction. The percentage of correct classifications obtained with the three different RPA were compared using the student t-test for proportions based on their SDs calculated as √ (p*(1-p)/N) where p is the proportion and N the sample size.

Statistical analysis was done with MATLAB (The Mathworks Inc, Natick, Massachusetts, USA) and JMP® 7.0.2 (SAS Institute, Cary, NC).

Results

Thirty-six men with LUTS were included in this study. The mean age was 67±9.3 y (range: 42-86), the mean BMI was 26.6±3.2 kg/m^2 (range: 21-34), the mean IPSS was 17±7 (range: 5-33), and the mean prostate volume was 52.6±33.2 cm^3 (range: 21-160). Twenty-eight patients (77%) had urodynamic obstruction, while eight patients (23%) were unobstructed. The median relative amplitudes of HHb were significantly higher in the obstructed group (*P* = 0.45). *Table 1* shows a comparison of NIRS, urodynamic and other relevant parameters between obstructed and unobstructed groups. *Figure 2* shows results of box-plot NIRS amplitudes of HHb, O_2Hb and Hb_{sum} based on presence or absence of obstruction.

Statistics (median)	Obstructed n = 28	Unobstructed n = 8	*P*-value*
Age (yr)	68 (52-86)	68.5 (42-76)	0.99
BMI (Kg/m^2)	26.5 (20-32)	26.6 (24-34)	0.69
IPSS	19 (7-28)	12 (5-33)	0.23
Prostate volume	42 (23-160)	32 (21-50)	0.15
Voided volumes	172 (16-600)	201 (97-424)	0.69
Q_{max} (ml/s)	5 (2-12)	7 (2-9)	0.69
$P_{det.Qmax}$ (cmH_2o)	69 (37-175)	39 (26-47)	0.005*
PVR (ml)	169 (0-682)	103 (0-350)	0.69
HHb (µmol/l)	1.8 (-4.0-6.2)	-4.5 (-5.6-2.1)	0.045*
O_2Hb (µmol/l)	1.1 (-5.8-7.5)	0.32 (-1.5-4.8)	0.09
Hb_{sum} (µmol/l)	2.6 (-9.0-9.5)	0.33 (-4.8-2.6)	0.23

Table 1. Comparison of demographic, urodynamic and near-infrared spectroscopy (NIRS) parameters between the obstructed and unobstructed groups.
BMI =body mass index, IPSS = international prostate symptom score, PSA = prostate specific antigen, Q_{max} = maximum flow rate, PVR = postvoid residual urine, HHb = deoxy-hemoglobin, O_2Hb = oxy-hemoglobin, Hb_{sum} = total hemoglobin (Hb_{sum} = HHb + O_2Hb), $P_{det.Qmax}$ = detrusor pressure at maximum flow rate. * *P*-value < 0.05 is significant (Mann Whitney U test).

Four of 36 patients had overt abdominal activity during voiding. Although this trend implies increased oxygen consumption or muscle fatigue during voiding in these patients, we tried to minimize any potential artifact in NIRS. Therefore, analysis was repeated after exclusion of these 4 patients. The median relative amplitude of HHb was still higher in the obstructed group (1.0 µmol/l, n= 25) than in the unobstructed group (-1.0 µmol/l, n = 7) but without statistical significance (P = 0.12)

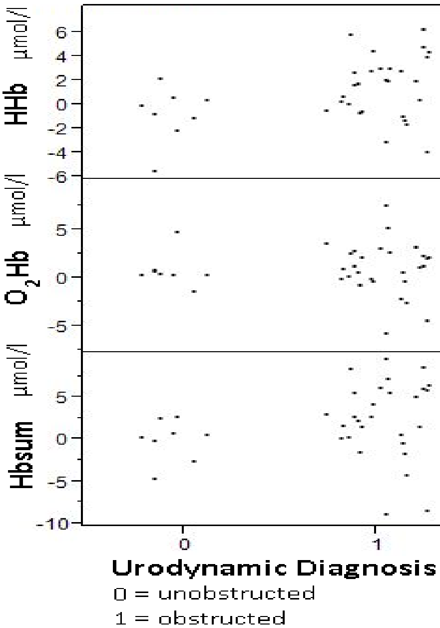

Figure 2. Scatter-Plot amplitudes of deoxy-hemoglobin (HHb), oxy-hemoglobin (O_2Hb), and total hemoglobin (Hb_{sum}) based on presence or absence of obstruction according to standard urodynamic diagnosis. Despite the overlapping, NIRS parameters were significantly higher in obstructed patients compared to unobstructed patients.

RPA of NIRS relative amplitudes revealed that NIRS correctly classified patients as obstructed or unobstructed in 32 of 36 patients (88%) with 96% sensitivity and 62% specificity, 90% PPV and 62% NPV for BOO [AUC: 0.92]. RPA of the combined Q_{max}, IPSS, PVR and prostate volume correctly classified 26 of 36 patients (72%) with 71% sensitivity and 75% specificity, 91% PPV, and 75% NPV for BOO [AUC: 0.84]. When NIRS amplitudes were added to this combination, RPA showed correct classification in 32 of 36 patients (88%) with 89.3% sensitivity and 87.5% specificity, 96.3% PPV, and 87.5% NPV for BOO [AUC: 0.96] This increase of percentage correct classifications was statistically significant (P<0.001). *Figure 3* shows the classification responses of this non-invasive combination; the computed probability of having the diagnosis 'obstructed' was 100% using the cut-off Hb_{sum} >= 2.6 µmol/l in 15 of 36 patients. For patients with Hb_{sum} amplitudes < 2.6 µmol/l the prostate volume was checked; a cut-off value >= 71 grams had a 100% probability to be obstructed in 5 of 36 patients. For patients with prostate volume < 71 grams, the IPSS was checked; an IPSS < 15 had a 0% probability of being obstructed in 5 of 36 patients. For patients with IPSS >= 15, the Q_{max} was checked; the Q_{max} cut-off value < 8 ml/s had a 100% probability of being obstructed in 5 of 36 patients while a Q_{max} >= 8 ml/s had a 62% probability of being obstructed in 3 of 36 patients.

Discussion

Qualitative NIRS has been applied in monitoring of bladder hemodynamic during voiding phase[7-9] and filling phase[12] of the micturition cycle. In the current study, relative changes in the concentration of hemoglobin in the bladder wall were quantified during the initial phase of detrusor muscle contraction until the point of Q_{max}. We believe it is the most active phase of voiding cycle with substantial hemodynamic changes are expected due to central and/or peripheral regulatory mechanisms of blood flow and the mechanical effect of contraction on the bladder wall vasculature (myogenic effect). NIRS measures changes in hemoglobin concentration and oxygen consumption in biological tissues mainly from the venous blood compartment[13-15]. Hemodynamic studies of skeletal muscles revealed that forceful contraction results in compression of the muscle vasculature with expulsion of the blood into the extra-muscular venous compartment 'muscle pump' effect[16]. The same would be true for detrusor muscle contraction during voiding. Therefore, a higher venous outflow would be expected in the obstructed group due to the more powerful contraction of the bladder exerted to overcome the high outlet resistance.

The median amplitude of change in HHb was significantly higher in the obstructed group. This overall trend may reflect a pathophysiologic phenomenon of increased oxygen extraction during more powerful detrusor muscle contraction with progressive muscle fatigue.

In spite of this overall trend of NIRS data to be higher in the obstructed group, there was some overlap between the obstructed and unobstructed groups as shown in *figure 2*. While Azadzoi *et al.*[18] observed a decrease in blood flow to the bladder wall during spontaneous and evoked contractions in animal studies. Kershen *et al.*[19] showed that the urinary blood flow is increased with increase in bladder pressure and volume, while Kroyer *et al*.[20] reported inconsistent variations in mucosal and muscular blood flow of the bladder with increased bladder pressure in dogs. In their experiment, the blood flow of the bladder was increased in one dog, decreased in another dog and showed no change in a third dog. Doppler ultrasound studies have shown a high arterial resistive index in patients with BOO[21-23]. These studies attributed their findings to ischemic changes in the bladder wall due to BOO. We think that time factor and chronicity of BOO needed to develop this proposed ischemia should be taken into account, meaning that it may not occur in patients with recent history of LUTS/BOO.

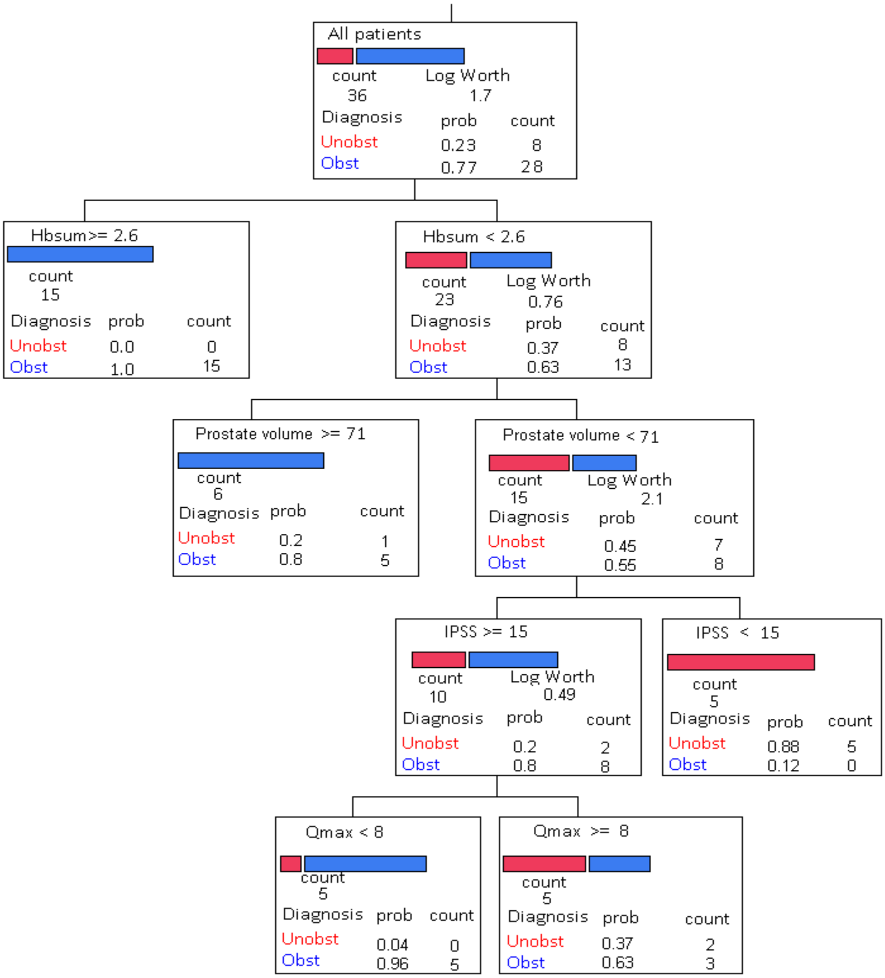

Figure 3. Classification responses of recursive partition analysis of the combined non-invasive parameters of near-infrared spectroscopy (NIRS), prostate volume, maximum flow rate (Q_{max}), and International Prostate Symptom Score (IPSS). $-\log_{10}$(p-value); Prob = probability of having the diagnosis either obstructed or unobstructed. Total number of patients is 36. Number of true positives is 25 of 28, number of false positives is 1 of 8, number of true negatives is 7 of 8, and number of false negatives is 3 of 28. The sensitivity and specificity for obstruction is 89.3% and 88%, respectively [AUC: 0.96]

NIRS in Men with LUTS

Our findings may explain the inconsistency in NIRS patterns reported by Chung *et al*.[24]; the authors applied a non-invasive diagnostic algorithm of Q_{max}, PVR and qualitative NIRS patterns during voiding in men with LUTS. This algorithm came with low diagnostic value for BOO [AUC: 0.48] and interestingly 35% of patients with BOO had a downward, 15% a flat and 50% an upward NIRS pattern. While 57% of patients with no BOO had a downward, 14% a flat and 29% of these patients had an upward NIRS pattern.

An exploratory analysis was further performed to explore potential usefulness of NIRS in clinical practice. Results of RPA using the relative amplitudes of NIRS revealed their ability to correctly classify 88% of patients. While correct classification using prostate volume, IPSS, PVR and Q_{max} was only in 72% of patients. This indicates that NIRS data would be of value in the diagnosis of BOO independently. When NIRS data were combined with other parameters, like prostate volume, IPSS PVR, and Q_{max}, it significantly improved their diagnostic performance to predict BOO. A classification model was developed combining all these parameters, the software found no suitable cut in a PVR parameter that matches the desired fit, and therefore, PVR was automatically excluded in this model. This model successfully classified 89% of patients with 89.3% sensitivity and 87.5% specificity, 96.3% PPV and 87.5% NPV for BOO [AUC: 0.96].

In previous work by Stothers *et al.*[8], the authors developed a classification and regression tree model using relative changes in the concentration of HHb and O_2Hb from start to end points of urinary outflow with high sensitivity (100%) and specificity (89%) of NIRS to BOO. The mathematical model applied in this study is fully described by Guevara *et al*.[25], which seems to be relatively difficult to comprehend and to use.

NIRS is susceptible to motion artifacts[26]. Abdominal straining can lead to exaggerated NIRS response[27]. Four patients were excluded due to overt abdominal activity during voiding. The median relative amplitude of HHb was still higher in the obstructed group but with no statistical significance, which implies a potential increase in oxygen consumption or detrusor muscle fatigue during voiding, and therefore such data can still be of value even though spikes due to motion artifacts occur in the P_{abd} curve. For optimal application of NIRS in clinical practice, we recommend a strict instruction to the patients to avoid using abdominal straining during the measurements. We also would suggest extra monitoring of abdominal muscles during measurements using accelerometry. Finally, algorithms to cancel motion artifacts in NIRS for monitoring of brain activity are currently available[28,29]. It will be of great value to develop such algorithms for NIRS in Urology.

A limitation in our study would be the difficulty to select the time window within which NIRS changes were quantified in future studies using NIRS alone. A solution would be to apply point ‘A’ as the point of first deviation from a stable baseline before the onset of urinary flow. Another limitation would be the relatively small sample size to run a RPA. The resulted algorithm needs to be validated in larger studies.

Conclusions

When applying NIRS in men with LUTS during voiding, there is an overall trend of the relative median amplitude of HHb to be higher in men with BOO. This seems to be of physiologic origin due to increased the amount of oxygen consumed during voiding. NIRS data can be of diagnostic value in men with LUTS. An algorithm is being developed in our series that would provide hemodynamic, anatomical and functional evaluation of the lower urinary tract. Moreover, it esteems the impact of BOO on the patient.

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CHAPTER 7

Noninvasive 2-Dimensional Monitoring of Strain in the Detrusor Muscle in Patients with Lower Urinary Tract Symptoms using Ultrasound Strain Imaging

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Abstract

Purpose

Pressure flow studies and filling cystometry are currently the standard diagnostic urodynamic tests for lower urinary tract symptoms. A non-invasive ultrasound based method for 2-dimensional monitoring of deformation (or strain) in the detrusor muscle may provide insight into detrusor muscle structural and dynamic properties related to pressure in physiological and disease conditions.

Materials and Methods

In a male patient population with lower urinary tract symptoms, strain in the detrusor muscle (perpendicular to the bladder wall) was estimated based on 2-dimensional radio frequency ultrasound imaging. The estimated strain was correlated to detrusor pressure and urinary flow rate using Spearman's correlation coefficient.

Results

Twenty men (mean $\pm$ SD age 66$\pm$6 years) with lower urinary tract symptoms were included in the study. Ultrasound data acquisition was successful in 13 patients. In 7 patients data acquisition failed due to out-of-plane motion of the bladder wall during voiding or as a result of patient movement during acquisition. The estimated strain correlated positively with detrusor pressure in the 5 patients with an isovolumetric detrusor contraction (Spearman's 0.70–0.99, $p < 0.05$). Of 8 patients with urinary voiding during detrusor muscle contraction this correlation was significantly positive in 5 patients (Spearman's 0.52–0.81, $p < 0.05$).

Conclusions

In 13 of 20 patients with lower urinary tract symptoms we demonstrated that strain in the detrusor muscle can be estimated using ultrasound imaging. The estimated strain correlated positively with the detrusor pressure. Optimal results were obtained in the pre-voiding phase, suggesting that ultrasound strain imaging can possibly be used to monitor detrusor muscle activity in real time.

The bladder is a hollow smooth muscular structure. The function of the bladder is to store urine at a low pressure and, when the subject finds it appropriate, expel the urine until complete emptying is achieved. This requires coordination between detrusor muscle contraction and urethral outlet complex relaxation[1]. Disturbances in this coordination lead to voiding dysfunction such as bladder outlet obstruction. BOO is characterized by an increase in detrusor pressure with a decreased urinary flow rate during voiding[2]. Of men older than 60 years 25% require surgical treatment for BOO[3]. A pressure flow study is the current standard diagnostic urodynamic test for BOO. It studies the relation between bladder contractility and the resulting urine flow output[4]. To perform a PFS, transurethral and rectal pressure measurement catheters are necessary to quantify p_{det}. The latter represents the component of the intravesical pressure (p_{ves}) that results from contraction of the detrusor muscle in the bladder wall. P_{det} is calculated by subtracting the abdominal pressure (measured with the rectal catheter) from p_{ves} (measured with the transurethral catheter)[2,5]. The urinary flow rate is measured using an external flowmeter. The invasive nature of PFS can lead to potential morbidities, such as urinary tract infections, discomfort and pain. Therefore, it is desirable to develop a non-invasive diagnostic technique to quantify detrusor muscle contractility. Such a non-invasive method could make diagnostic procedures more patient friendly. With ultrasound imaging it is possible to estimate deformation in biological tissues[6]. This deformation can be passive (as a result of applying an external compression) or active (in the case of a muscle contraction). This technique has been applied in dynamic monitoring of local skeletal muscle strain during contraction[7]. In the current study ultrasound technology was applied to measure deformation of the detrusor muscle (strain) during and before the voiding phase. The hypothesis for the study was that for an increase in detrusor pressure the detrusor muscle needs to contract and that these contractions result in a change in muscle thickness. Monitoring this deformation may provide a clue to understanding the mechanisms of p_{ves} production in relation to detrusor muscle structural and dynamic properties in physiological and disease conditions.

Patients and Methods

Patient Population

A total of 20 male patients with LUTS, referred to the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, for urodynamic investigations were included in the study. The research was performed in accordance with the Declaration of Helsinki of the World Medical Association[8] and was approved by the local ethical committee. Inclusion criteria were men older than 45 years with LUTS. Exclusion criteria were men with neurogenic voiding dysfunction, urinary tract infection, hematuria, previous radical prostatectomy or TURP. All 20 patients signed an informed consent.

Data Acquisition

All 20 patients underwent standard PFS (MMS Medical Measurement Systems, Enschede, The Netherlands). The prostate volume was measured using transrectal ultrasound and PVR was measured using a transurethral catheter. During voiding, RF ultrasound data were acquired using a SONOS® 7500 ultrasound system equipped with a linear array transducer, 11-3L, f_c 7.5 MHz. At the end of the PF and just before the patient was given the command to void, the transducer was placed transversal above the pubic bone. Before placement a sufficient amount of ultrasound gel was applied on the skin and the transducer was placed gently in a stable manner to prevent unnecessary pressure application and potential affection of the bladder function. At each ultrasound recording the detrusor was identified as a delineated structure[9]. The urinary flow and p_{det} were recorded simultaneously using standard urodynamic equipment (*figure 1*). At the onset of an increase in p_{det}, approximately 20 seconds of ultrasound data were acquired prospectively at a frame rate of 2 Hz (2 patients) and 5 Hz (18 patients), and stored for offline analysis. The ultrasound data that corresponded to the increase in p_{det} toward the opening pressure were selected for further analysis.

Data Analysis

In each recording a ROI was selected that encompassed the detrusor muscle. To make sure that data analysis is performed on the same part of the detrusor muscle during the voiding cycle, the location of the ROI was corrected for axial and lateral movement of the bladder wall during acquisition using a tracking algorithm[10]. The deformation was estimated using a coarse-to-fine normalized cross correlation based strain algorithm[11]. A short explanation of this technique is presented in *figure 2*. The first (coarse) iteration was based on the envelope of the raw RF signals. The envelope was calculated by demodulation of the RF signals, i.e. the absolute value of the Hilbert transform of the RF signals. The following iterations (fine) were based on the raw RF signals. After each iteration, the estimated displacements were median filtered to reduce the accumulation of noise in the final displacement estimate. To improve the final displacement estimate, local aligning and temporal stretching were applied[12]. Subsequently the axial strain was derived from the displacements using 2D least squares strain estimators[13]. In the resulting 2D elastogram we calculated the mean and SD. The strain between the sequential ultrasound frames was then accumulated with respect to the first acquired frame, i.e. a previous muscle status. From each cumulative strain curve we identified ε_{max} and from the urodynamic measurements we measured p_{det} at the maximum strain and p_{det} at the first acquired ultrasound frame. From these 2 values we calculated the change in detrusor pressure at maximum strain ($\Delta p_{det}@\varepsilon_{max}$) with respect to the first acquired ultrasound frame (*figure 1*). The estimated axial strain in the detrusor muscle was correlated to p_{det} and Q_{ura} using Spearman's correlation coefficient.

Results

Twenty patients with LUTS were included in the study. The demographic and urodynamic data and post-measurement treatment modality are shown in *table 1*. Urodynamic/clinical diagnosis and treatment modality for individual patients are shown in *table 2*. In 7 patients the acquisition of ultrasound data failed due to out-of-plane motion of the bladder wall during voiding or as a result of patient movement during acquisition.

In 5 patients ultrasound data were acquired during an isovolumetric contraction (i.e. an increase in detrusor pressure without urinary flow) in the prevoiding phase. All 5 patients with isovolumetric contraction voided after the ultrasound data acquisition. In all 5 patients the axial strain showed a significantly positive correlation with p_{det} (Spearman's coefficient 0.70–0.99, $p < 0.05$). An example of strain in the detrusor during an isovolumetric contraction is shown in *figure 3*. In 8 patients ultrasound data were acquired during a part of the voiding phase in which there was an increase in detrusor pressure and urinary flow. In 5 of these 8 patients we found a significant positive correlation between the cumulative axial strain in the detrusor muscle and p_{det} (Spearman's coefficient 0.52–0.81, $p < 0.05$). One patient displayed a significant negative correlation and 2 patients showed a non-significant correlation. Also in 6 of these 8 patients we found a significant positive correlation between the axial strain and urinary flow (Spearman's coefficient 0.32–0.90, $p < 0.05$). In 1 patient this correlation was non-significant and in 1 there was a significant negative correlation (same patient as for p_{det}). A typical example of strain in the detrusor muscle during voiding is shown in *figure 4*. From the 13 patients with a successful ultrasound acquisition the maximum strain (ε_{max}) is plotted versus the change in detrusor pressure at the maximum strain ($\Delta p_{det}@\varepsilon_{max}$) as presented in *figure 5*. The isovolumic and the non-isovolumic cases are indicated by open and closed circles, respectively.

Discussion

In this study we presented preliminary data on strain in the detrusor muscle estimated from ultrasound imaging and postulated as an indication of detrusor contractility. In the 5 patients without urinary flow (isovolumetric contraction), as shown in *figure 3*, strain in the detrusor muscle was observed to increase with an increase in p_{det}. This measurement indicates that the thickening of the detrusor muscle is possibly related to the contraction of the muscle. Also, in these patients the correlation coefficient was higher than in the patients who showed an increase in urinary flow rate simultaneous with a detrusor pressure increase.

Table 1. Demographic and urodynamic data

	Mean	Median	SD	Min	Max
Age	66.9	66.0	6.5	54	82
Body mass index (kg/m2)	25.5	25.1	4.3	16.0	34.7
Prostate volume (cc)	83	63	66	19	296
International prostate symptom score	17	17	8	1	31
Detrusor opening pressure (cm H_2O)	83	73	35	41	153
P_{det} at max flow rate (cm H_2O)	76	67	30	40	129
Free flow voided volume (ml)	175	137	209	0	935
Free flow max flow rate (ml/sec)	7.70	7.50	5.0	0	17
Free flow PVR (ml)	125	97	134	2	501
PFS voided volume (ml)	206	208	175	0	652
PFS max flow rate (ml/sec)	5.7	5.5	4.1	0	14
PFS PVR (cc)	169	57	198	3	604

A second plausible explanation for the thickening of the detrusor muscle could be the change of volume in the bladder as a result of voiding. A positive correlation with the urinary flow rate was observed in those patients in whom the correlation with the detrusor pressure was positive. An example, in which an increase in detrusor pressure is accompanied by an increase in urinary flow rate, is shown in *figure 4*. In these cases the correlation coefficient was lower than in the isovolumic cases. The findings in the (non)-isovolumic cases indicate that contraction of the detrusor muscle and change in bladder volume contribute to the measured strain in the detrusor muscle. It appears that the change in bladder volume also affects the measured strain and, thus, that the estimated detrusor muscle deformation is related to the combination of active muscle contraction and to volume change caused by voiding. This may reveal the importance of exploring the contribution of isovolumetric intravesical pressure in changing the detrusor strain and the effect of volume change on the amount and pattern of detrusor strain. Further (in vitro) investigation may provide more information to understand the links among volume change, muscle contraction and the measured strain.

Table 2. Urodynamic diagnosis and treatment modality in individual patients

Pt No	BOO	Treatment
1	Pos	TURP
2	Pos	TURP
3	Neg	Watchful waiting
4	Pos	Alpha blocker
5	Pos	On list for green light laser
6	Neg	Watchful waiting
7	Pos	TURP
8	Neg	Alpha blocker
9	Pos	Green light laser prostatectomy
10	Pos	On list for green light laser
11	Pos	Clean intermittent self-catheterization
12	Pos	Open prostatectomy
13	Pos	Green light laser prostatectomy
14	Pos	Alpha blocker
15	Pos	On list for TURP or green light laser prostatectomy
16	Pos	Transurethral microwave therapy
17	Pos	Green light laser prostatectomy
18	Pos	Green light laser prostatectomy
19	Neg	Alpha blocker
20	Pos	On list for green light laser

Theoretically, the best correlation between strain and pressure will be present during the pre-voiding phase. The reasoning is that during the pre-voiding phase the detrusor muscle contracts, which results in an increase in intravesical pressure without volume change. In the patient with a significant negative correlation between detrusor strain and detrusor pressure, we measured a peak flow rate of 10 ml per second with a small increase in detrusor pressure (Δp_{det} 10 cm H_2O) during the period of data acquisition. Such a change in volume could result in movement of the bladder wall, resulting in decorrelation of the RF signals and in an erroneous negative correlation. Previous to the urinary flow we did observe an increase in detrusor strain (ε_{max} 8.8%) with a non varying p_{det} of 70 cm H2O since the start of the data acquisition. However, as soon as voiding started the estimated strain collapsed. This is probably the result of out-of-plane motion of the bladder wall during data acquisition. To our knowledge, this is the first study to monitor detrusor muscle activity before and during voiding using ultrasonography. The strain in the detrusor muscle showed a positive trend with detrusor pressure in the 13 successful ultrasound acquisitions. The presented values of strain were cumulated with respect to the first acquired ultrasound image. Therefore, an increase in axial strain indicates thickening of the detrusor muscle with respect to a baseline muscle status, whereas a decrease indicates compression of the detrusor muscle.

In 7 patients tracking of the bladder wall failed. The most common cause of this failure was out-of plane motion of the bladder wall during voiding or as a result of patient movement during acquisition. A possible solution for this out-plane-motion problem could be the extension of the data acquisition from 2 to 3 dimensions. Another cause was the challenge for the urologist to get the bladder wall adequately and in time in the imaging plane of the transducer. There was only a limited time window to place the transducer and find the bladder wall before the patient started to void. With the progression of the study the success rate of the ultrasound acquisitions increased. Another parameter to consider is the frame rate of data acquisition. The frame rate was set at 5 Hz in 18 patients and at 2 Hz in 2 patients. The latter frame rate increased the length of data acquisition but also decreased the correlation of ultrasound signals between sequential frames. The reduced frame rate also reduced the refresh rate of the image on the ultrasound system. This reduced refresh rate posed an extra challenge for the urologist to find and to keep the bladder wall in the imaging plane of the transducer. Therefore, a frame rate of 5 Hz was preferred. The selection of the frame rate to be used resulted from a trade-off between the applicability of the technique for the urologist and the time window (in seconds) that could be acquired. The cause of this trade-off is the limited system data memory that limits the number of RF ultrasound frames that could be acquired. An increase in this data memory could, for example, extend the number of acquirable frames.

At the current stage of this study we are working on extending the time window from a limited 5 seconds to 30 to 50 seconds, which will be of great value to obtain an optimal understanding of the dynamics of voiding by studying detrusor strain in a complete voiding cycle. Thus, ultrasound strain imaging could possibly be used as an indication of muscle contraction in the diagnosis of BOO. Most previous studies to develop non-invasive diagnostic techniques for BOO in patients with LUTS examined static parameters such as ultrasonographic measurement of detrusor wall thickness[14] or bladder weight[15]. Other trials investigated dynamic parameters during voiding such as perineal noise recording[16,17] and color Doppler urinary flow velocity[18] or near-infrared spectroscopy[19]. However these studies were lacking the information about detrusor contractility. This is important to avoid undiagnosed detrusor hypocontractility, especially if surgical interference is to be considered[20]. For a long time this made conventional PFS the gold standard diagnostic technique for BOO in patients with LUTS. Ultrasonic monitoring of detrusor muscle contractility presents the first direct non-invasive approach to quantify detrusor contractility before voiding. This approach can be of great usefulness in the assessment of detrusor muscle structural and dynamic properties in relation to its function in health and disease conditions. This assessment can then be performed without the necessity of an invasive PFS with the potential morbidities of discomfort, pain and urinary tract infection.

Conclusions

In 13 of 20 patients with LUTS we showed that strain in the detrusor can be estimated using ultrasound imaging. The estimated strain correlated positively with the detrusor pressure in the pre-voiding phase. This suggests that ultrasound strain imaging can possibly be used to monitor detrusor muscle activity in real time.

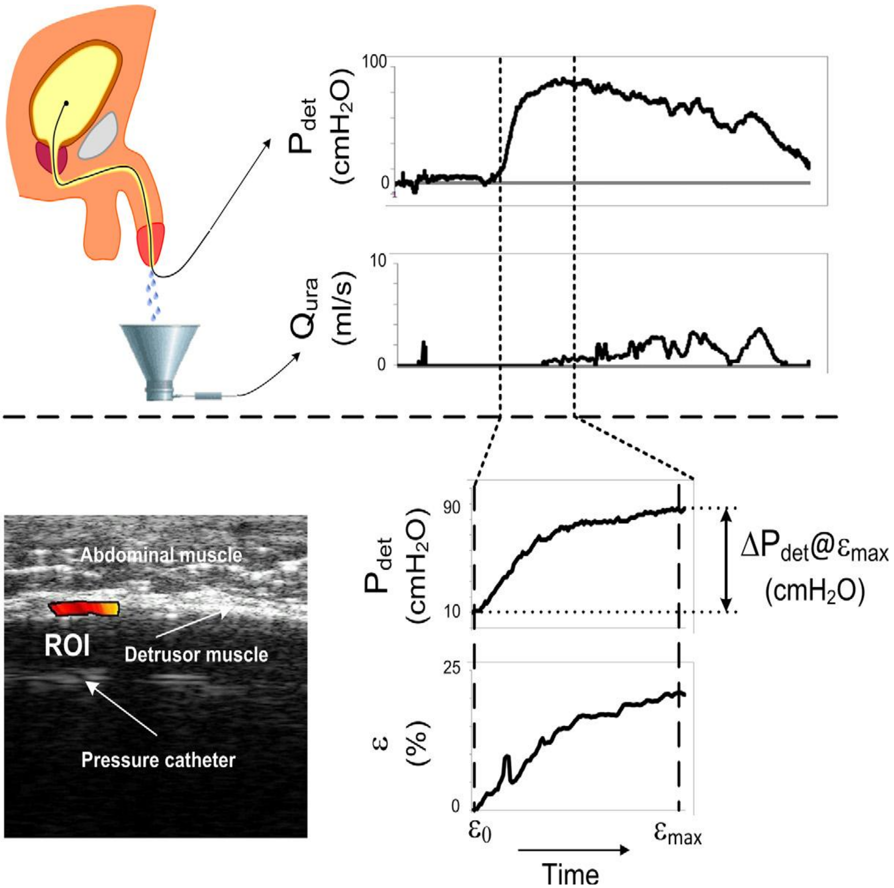

Figure 1. Analysis of urodynamic signals and ultrasound imaging. At onset of voiding (increase in p_{det}) ultrasound data acquisition started. From ultrasound data cumulative axial strain was derived in selected ROI and maximum axial strain (ε_{max}) was identified. Detrusor pressure at maximum strain (ε_{max}) and detrusor pressure at start of acquisition (ε_0) were identified in urodynamic signals, and used to calculate change in detrusor pressure at maximum strain.

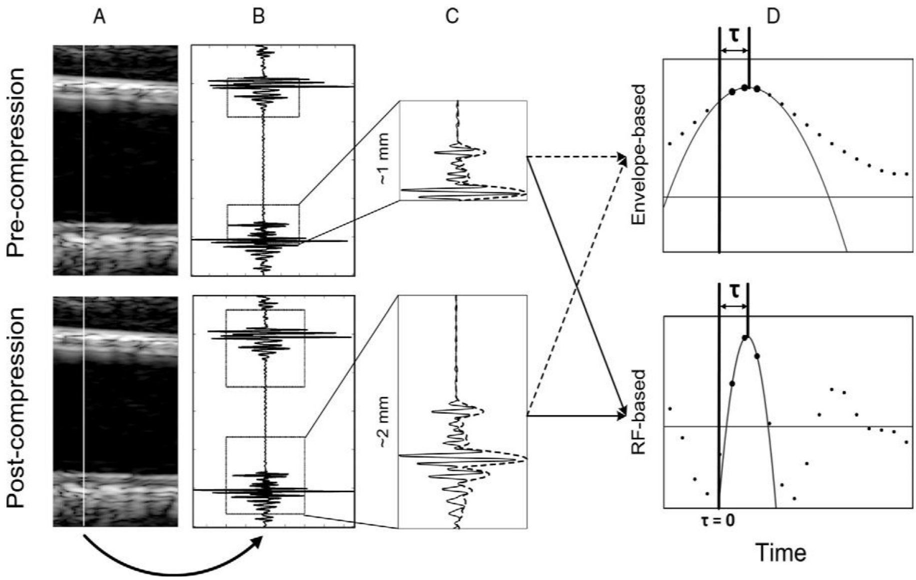

Figure 2. Estimation of time delay _ from RF ultrasound line before and after deformation. From B-mode images (*A*) RF line is selected (*B*). Region of approximately 1 mm around is selected in pre-deformation line and of approximately 2 mm is selected in post deformation line (*C*). Then 2 regions are cross-correlated between RF line before and after deformation (*D*). One cross- correlation function is calculated from envelope of RF signal (broken line) and one from RF line (solid line). Through maximum of cross-correlation function and points left and right of maximum, parabolic function is fitted to achieve sub pixel accuracy in estimation of time delay. Time delay multiplied by speed of sound in tissue results in displacement estimate of selected region.

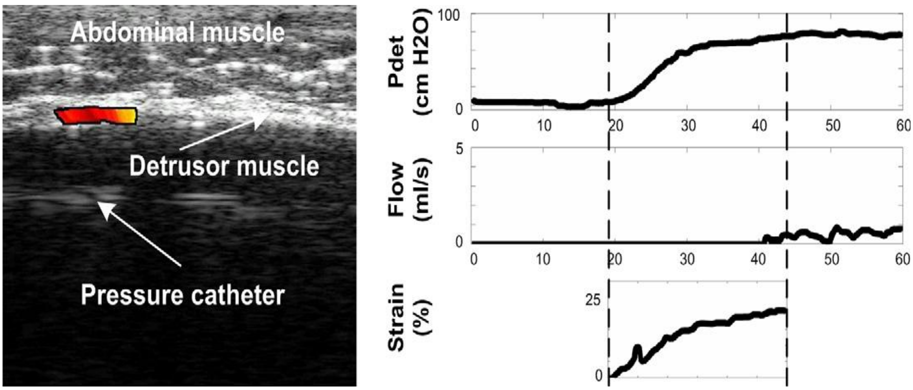

Figure 3. Example of axial strain in detrusor muscle in patient with isovolumetric contraction of detrusor muscle. Axial strain increases with increase in detrusor pressure without any change in bladder volume.

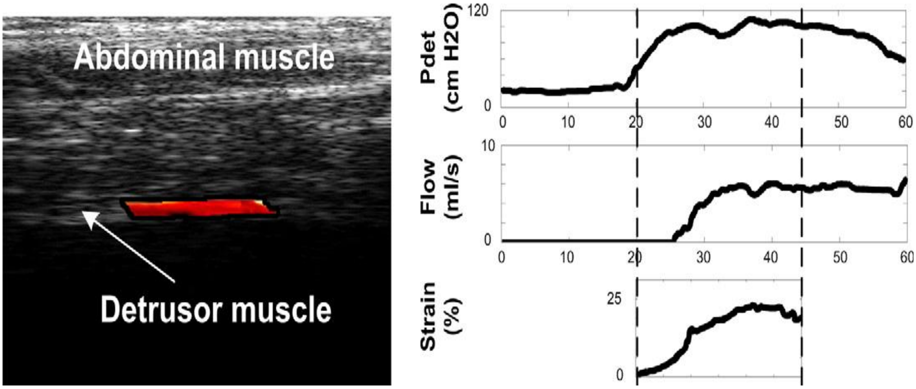

Figure 4. Example of axial strain in detrusor muscle in patient with increase in Q_{ura} simultaneous with increase in detrusor pressure. Axial strain increases with increase in detrusor pressure accompanied by change in bladder volume.

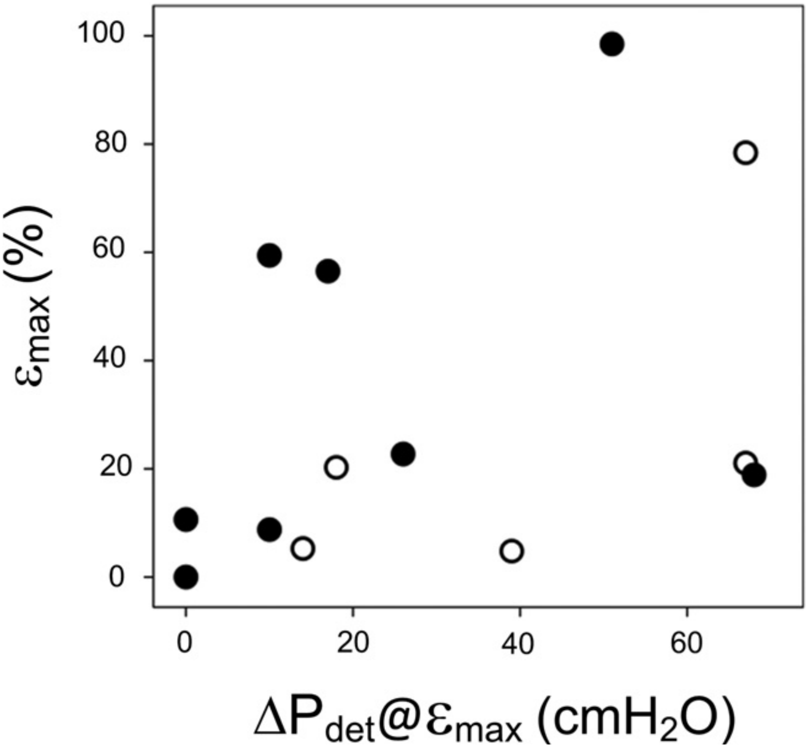

Figure 5. Detrusor pressure change between start of ultrasound data acquisition and point of maximum strain as function of maximum strain. Open circles represent patients with isovolumetric contraction and closed circles represent those with non-isovolumetric contraction.

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SUMMARY AND FUTURE DIRECTIONS

Summary

Filling cystometry is currently the standard diagnostic test for detrusor overactivity (DO) in patients with overactive bladder symptoms (OAB). Pressure flow study (PFS) is the standard test for the diagnosis of bladder outlet obstruction (BOO) in patients with voiding lower urinary tract symptoms (LUTS). However, these tests are invasive and can cause potential morbidities, such as urinary tract infections, discomfort and pain.

Therefore, in this thesis we described new non-invasive techniques for mentoring of bladder activity in patients with functional lower urinary tract disorders in both filling and voiding phases.

In **chapters 1 and 4** reviewing the literature of the clinical studies that have been performed to develop non-invasive diagnostic tools for storage phase disorders revealed that the ultrasonographic parameters, such as bladder wall thickness (BWT), detrusor wall thickness (DWT) and ultrasound estimated bladder weight (UEBW) have been examined as surrogates for DO in patients with OAB syndrome. Only few studies could present potential diagnostic cut-offs for DO. However, these studies showed that

the methodology is not always consistent and not very standardized. Studies that investigated laboratory biomarkers such as nerve growth factor showed substantial correlation with DO and/or OAB, but with low specificity for DO as it can be increased in response to BOO, interstitial cystitis and prostatitis. In conclusion, the above-mentioned techniques cannot be applied reliably in routine clinical practice yet.

Clinical studies that have been done to develop non-invasive diagnostic tools for voiding phase disorders, namely BOO, in men with voiding LUTS followed two approaches: The first approach was indirect measurement of the isovolumetric bladder pressure during voiding, which showed good accuracy as compared to the conventional PFS. We think that estimation of the abdominal pressure contribution and its impact on the results will add more value to this technique. The second approach was ultrasonographic measurement of non-urodynamic parameters, such as BWT, DWT and UEWB, these parameters showed good correlation to BOO with some cut-offs for BOO diagnosis were developed and recently, guidelines have been proposed to standardize these measurements.

Other techniques of Doppler ultrasound urinary flow velocity measurement, perineal sound recording, near-infrared spectroscopy (NIRS), and Doppler resistive index of bladder wall arteries all show growing evidence, but their reproducibility still needs to be tested in larger patients study groups. Studies that combined various non-urodynamic parameters improved their diagnostic performance statistically. However, these parameters were diverse regarding the pathophysiological and clinical concerns. NIRS detects the hemodynamic changes caused by detrusor contractions. However, more basic and clinical studies are needed to evaluate the independent value of this technology in the non-invasive diagnosis of BOO.

NIRS is an optical technology. NIRS of biological tissues enables non-invasive evaluation of oxygen dependent hemodynamic changes in these tissues via measurement of the relevant changes in the concentration of hemoglobin. Oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (HHb) represent the oxygen supply and consumption of the tissue under monitoring, respectively. The sum of O_2Hb and HHb is Hb_{sum}, it represents the total blood perfusion of this tissue.

In **chapter 2** we explored the feasibility of NIRS to detect the hemodynamic effect of DO during filling cystometry. Our theory was that NIRS can detect the changes in oxygen supply and oxygen consumption of the bladder wall during DO. NIRS curves demonstrated apparently significant deviation from baseline concomitant with the start of DO in 35 of 39 occasions; all deviations occurred within the time period of the IDC. The median detrusor pressure at maximum flow rate in DO episodes without significant deviations in NIRS was lower than in those with significant deviations. NIRS could identify 90% of DO episodes via detection of their concomitant imprint on NIRS signals.

We proposed three possible explanations for the effects of DO on NIRS imprint. The first possibility is an autogenic hemodynamic phenomenon of DO. The second possibility is a compressive pattern of bladder wall vessels due to the sudden contraction during DO. The last possibility is an expected movement of the whole bladder wall with its vascular content during the DO, leading to substantial change in the volume of blood crossing the imaging scale of NIRS.

To check for the presence of motion artifacts in NIRS curves, we used the extra surface EMG monitoring of the abdominal wall muscles. Eleven of the 35 DO with concomitant deviations in NIRS curves had motion artifacts, either due to change in patient position during the session or due to their trials to withhold urine at moments of urgency during the DO.

It could be argued that the urodynamicists, while gauging the NIRS traces, were aware of the pressure and flow events of the corresponding cystometry channels. Therefore, to have more blinded methodology, this point was considered on conducting the larger study described in chapter 3.

In **chapter 3** we determined the reproducibility and accuracy of NIRS in the diagnosis of DO in a larger group of patients with OAB syndrome. Three urodynamicists were asked to identify deviations in NIRS at the time of DO. Agreement among the urodynamicists was ‘almost perfect’ for cystometry, while it was ‘substantial’ for NIRS. We think this can be explained by the familiarity of the urodynamicists with the classic setup of the conventional cystometry.

NIRS was highly sensitive to detect DO episodes: 92% for Hb_{sum}, 82% for O_2Hb and 78% for HHb. Hb_{sum} curve being the sum of O_2Hb and HHb can explain its higher sensitivity for DO. NIRS curves had a good diagnostic performance as predictors of DO, giving a range of AUC values of 0.80–0.85

for O_2Hb curves, 0.73–0.84 for HHb curves and 0.80–0.82 for Hb_{sum} curves, as calculated for the three observers. The overall specificity of NIRS parameters for DO was 86% for O_2Hb, 80% for HHb, and 72% for Hb_{sum}. The sensitivity and specificity were high in this study because they were tested in a data sample after exclusion of cases with motion artifacts. However, the situation should be different when the clinical applicability of NIRS will be addressed.

The two above-mentioned exploratory studies conducted at the Department of Urology of the Radboud University Nijmegen Medical Centre revealed that NIRS curves correlate well with DO episodes detected by conventional urodynamics. NIRS detects the hemodynamic changes caused by detrusor contractions. This implies that NIRS can be used to study the regulatory mechanisms of blood perfusion to the bladder during filling as well as the hemodynamic phenomenon accompanying DO. NIRS is a reproducible, non-invasive potential diagnostic tool, with high sensitivity for DO in patients with OAB symptoms. However, its value in clinical practice remains to be determined.

In **chapter 5** the applicability and accuracy of multiple uroflowmetry measurements using a new disposable home-based urinary flowmeter (Q_{Single}) in the diagnosis and management of men with LUTS were explored. The diagnostic performance of this new method was compared to measurements with home-based digital device and compared to single clinical measurement. This was a prospective, multicentre study. The mean Q_{max} obtained using Q_{Single} device did not differ from that obtained with clinic method.

While it was significantly higher for the digital device, mean voided volumes recorded with each device differed marginally. Patients reported good handling capabilities using the Q_{Single} device. It is concluded that applying this new home-based uroflowmetry can offer an easy and viable alternative of comparable accuracy to reduce the number of visits to the clinic in the follow-up and management of patients with LUTS.

Chapter 6 presents results of an application of a quantitative approach of NIRS in monitoring of voiding activity in 36 men with LUTS suggestive of obstruction. An algorithm was developed that combined quantitative NIRS with other non-invasive parameters of ultrasonographic measurement of the prostate volume, International Prostate Symptom Score (IPSS), PVR and Q_{max}. Raw NIRS data were used for quantifying amplitudes of change in the concentration of HHb, O_2Hb and Hb_{sum} in the bladder wall during voiding activity in relation to changes in detrusor pressure.

The hypothesis was that detrusor muscle contraction during voiding requires energy production with expected increase in oxygen demands and consumption. Results of PFS with simultaneous NIRS of the bladder during voiding revealed that the median amplitude of change in HHb was significantly higher in the obstructed group, which reflects higher oxygen consumption of the bladder wall during voiding. Patients were classified as obstructed or unobstructed based on detrusor/flow plot according to Griffiths. Recursive partition analysis (RPA) using amplitudes of change in HHb, O_2Hb and Hb_{sum} revealed the ability of NIRS to predict obstruction with 96% sensitivity and 62% specificity for BOO. However, 4 patients (12%) were misclassified.

When RPA was done using other non-invasive parameters, like prostate volume, IPSS, PVR and Q_{max}, this combination revealed a misclassification of 10 patients (28%) with 71% sensitivity for BOO. This indicates that NIRS showed better prediction of BOO than the other non-invasive parameters in our series. When NIRS parameters were combined with other non-invasive parameters of prostate size, IPSS, PVR and Q_{max} NIRS significantly (P = 0.001) improved their low diagnostic performance to predict BOO. A reclassification model was developed combining all these parameters. This model successfully reclassified patients in our series with 89.3% sensitivity and 88% specificity for BOO [AUC: 0.96].

The algorithm combining NIRS, prostate volume, IPSS and Q_{max} is not only a non-invasive diagnostic method of BOO, but also provides hemodynamic, anatomical, and functional evaluation of the lower urinary tract. Moreover, it takes in consideration the impact of BOO on the patient. Therefore, our algorithm can be a valuable alternative to other invasive and non-invasive diagnostic tools for BOO.

In **chapter 7** we presented the results of an experiment to quantify the detrusor muscle strain during voiding using the 2D ultrasonography. It is the first direct non-invasive approach to quantify detrusor contractility before voiding. This approach can be of great usefulness in assessment of detrusor muscle structural and dynamic properties in relation to its function in health and disease. Though the primary results are relatively promising as we could prove - in most cases - that detrusor strain significantly with the change in detrusor pressure, a more extended time window of measurement that covers the whole voiding activity would be more informative.

Currently, trials are done at our center to extend the time window from a limited 5 s. to be 30 to 50 s., which will be of great value to obtain optimal understanding of the dynamics of voiding by studying detrusor strain in a complete voiding cycle and to conclude the actual value of this technique in the diagnosis of voiding dysfunctions. Out-plane-motion problem could be the extension of the data acquisition from 2D to 3D.

Future directions

Routine diagnostic approaches for functional lower urinary tract disorders are: history taking from the patient, voiding diaries, Urgency Severity Scores, IPSS, Quality of Life questionnaires, clinical examination, cystoscopy and uroflowmetry.

Conventional filling cystometry and pressure flow studies are currently the standard tools for voiding LUTS and OAB symptoms. These tools necessitate insertion of transurethral and rectal catheters. Therefore, it is invasive and potentially morbid and it does not seem to be possible - at least in the near future - to avoid using these catheters to lessen the invasiveness conventional of urodynamics.

What are the key parameters in the diagnosis of voiding LUTS and/or OAB symptoms? If we answer this question we will be able to understand the rational of non-invasive urodynamics. Urodynamics estimates the pressure changes inside the bladder and abdomen to conclude: detrusor muscle compliance, the abrupt increase in detrusor pressure during DO and pressure exerted by detrusor pressure to void against bladder outlet resistance.

Over the last few decades, efforts have been directed towards development of various urodynamic and non-urodynamic approaches to estimate directly or –most of the time - indirectly functional and anatomical changes in detrusor muscle all over the voiding cycles. An example of urodynamic non-invasive approaches is the measurement of isovolumetric vesical pressure using penile cuff method. Non-urodynamic approaches can be classified as imaging approaches like ultrasonic measurement of BWT, DWT and UEBW, and laboratory approaches like estimation of urinary NGF and other neurotrophins.

In this thesis, we presented two novel imaging approaches to monitor storage and voiding phase events, applying two different technologies: NIRS of the bladder in patients with voiding LUTS and patients with OAB symptoms, and 2D ultrasonography in monitoring of voiding activity in men with LUTS. Our thesis presented also for an interesting home-based urinary flowmeter as a non-invasive tool to measure urinary flow parameters.

NIRS can detect the hemodynamic effects of bladder contractions, either involuntary contractions during filling, or voluntary contractions during voiding. Therefore, NIRS can indirectly indicate the presence of abnormal bladder activity during filling, namely DO.

NIRS showed high sensitivity and specificity for DO in clean data sample without motion artifacts. In addition to its potential independent diagnostic ability for some functional lower urinary tract disorders, such as DO and BOO, NIRS can provide adjuvant hemodynamic evaluation of these disorders. This advantage can open the way for the development of new diagnostic and treatment strategies for these disorders based on hemodynamic pathophysiological aspects. NIRS was successfully combined with some other parameters of prostate volume, IPSS, and maximum flow rate in the diagnosis of BOO in men with voiding LUTS.

2D ultrasonography and its novel application in monitoring of bladder activities, gave a direct access for the first time to monitor dynamic changes in bladder wall and specifically the detrusor muscle component. All previous imaging approaches were concerned with static measurement of BWT, DWT and UEBW, as indications for bladder hypertrophy in response to DO and/or BOO. Our results indicate a considerable correlation between detrusor strain measured by 2D ultrasonography and detrusor pressure. Therefore, we try to explore the possibility of replacing the invasive urodynamic measurement of detrusor pressure by 2D ultrasonographic estimation of detrusor strain in the near future.

Some limitations emerged during developing our NIRS and 2D ultrasonography techniques: importantly, NIRS susceptibility to motion artifacts and the limited time window for 2D monitoring of detrusor activity.

Future studies should investigate the possibility of developing algorithms to cancel motion artifacts in NIRS in order to introduce this promising technique as a non-invasive diagnostic tool for DO and/or BOO in clinical practice. EMG or accelerometry of the abdominal muscles could be a useful tool to monitor the effect of abdominal activity during NIRS measurements. Some more technical work is needed to extend the time window of measurement to cover the whole act of voiding. Out-plane-motion problems could be the extension of the data acquisition from 2D to 3D.

The home-based Q_{Single} flowmetry device showed comparable results to the standard clinic-based method. It is easy to manage by patients in their own environment with the potential to reduce the number of clinic visits.

When the clinical setup and reproducibility of NIRS and 2D sonographic measurement of detrusor strain techniques described in our thesis are well established they will become reliable, independent, diagnostic tools - or at least - a useful screening tool for BOO and DO in patients with functional lower urinary tract disorders.

Various combinations of non-invasive diagnostic tools could be of high value in clinical setup for functional lower urinary tract disorders. Sonographic measurement of BWT with NIRS monitoring of the bladder activity could give valuable insight to the correlation between the hypertrophic and the vascular changes of the bladder wall due to BOO or DO.

2D ultrasonographic estimation of detrusor strain can be combined with uroflowmetry and new nomograms could be developed plotting 2D detrusor strain versus flow rate values in the diagnosis of BOO.

We are currently developing qualitative and quantitative NIRS and 2D sonographic parameters to predict BOO and DO. A small wireless NIRS or bladder-scan devices would be placed over the bladder in combination with a home-based flowmeter will be the future setup of a small functional urology unit. Moreover, smart phone and tablet devices applications can be designed for more public and convenient use of our novel diagnostic tools. There would be a possibility of having a smart toilet supplied with NIRS, 2D ultrasound and a flowmeter. Data collected from patients at home will be easily transferred to a remote-processing computer for the convenience of the patients.

Future directions should also explore the possibility of recording changes in the intravesical pressure. It is obvious that all above-mentioned studies tried to approach this important parameter either in a direct or indirect way, for example, it could be interesting to develop a device that records intravesical changes similar to the one used by ophthalmologists. Presence of such a device can lead to jump in the field of urodynamics when NIRS and 2D ultrasound will be combined with a home-based flowmeter to replace the conventional urodynamics.

SAMENVATTING

Urodynamica omvat de gestandaardiseerde diagnostiek voor afwijkingen en ziektes aan het urinestelsel. Deze is invasief te noemen en kan zodoende pijn en ongerief bij de patiënt veroorzaken. Deze thesis beschrijft nieuwe innovatieve en niet-invasieve urodynamische technieken ter monitoring van de blaasactiviteit in patiënten met functionele afwijkingen aan het urinewegstelsel.

Zowel **hoofdstuk 1 en 4** beschrijven literatuuroverzichten van de klinische studies die zijn uitgevoerd voor de ontwikkeling van niet-invasieve diagnostische instrumenten voor functionele afwijkingen aan het urinewegstelsel.

In **hoofdstuk 2** is de haalbaarheid onderzocht van de toepassing van near-infrared spectroscopie (NIRS) in de detectie van het hemodynamische effect van detrusor overactiviteit (DO) gedurende cystometrie. De theorie behelst dat NIRS de veranderingen in zuurstofvoorziening en zuurstofconsumptie in de blaaswand kan detecteren gedurende DO.

Hoofdstuk 3 beschrijft de reproduceerbaarheid en nauwkeurigheid van NIRS in de diagnose van DO in een grote groep patiënten met overactieve blaas (OAB) syndroom.

Hoofdstuk 5 omschrijft de toepasbaarheid en nauwkeurigheid van meerdere uroflowmetrische metingen met een nieuwe disposable flowmeter in de diagnose en aansturing van mannen met lagere urine traject symptomen (LUTS).

In **hoofdstuk 6** worden de resultaten gepresenteerd van de applicatie van een kwantitatieve aanpak van NIRS in de monitoring van blaaslediging in 36 mannen met LUTS. Er is een algoritme ontwikkeld dat kwantitatieve NIRS combineert met andere niet-invasieve parameters, zoals ultrasonografische metingen van het prostaat volume, de Internationale Prostaat Symptoom Score (IPSS), PVR en Q_{max}. Ruwe NIRS data zijn gebruikt ter kwantificering van de amplitudeveranderingen van HHb, O_2Hb en Hb_{sum} in de blaaswand gedurende blaaslediging in relatie tot veranderingen in de detrusordruk.

Hoofdstuk 7 geeft de resultaten van een experiment ter kwantificatie van de rek in de detrusorspier gedurende blaaslediging met 2D ultrasonografie. Dit is de eerste niet-invasieve aanpak tot kwantificatie van detrusorcontractie voordat blaaslediging plaatsvindt.

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BIOGRAPHY

Fawzy Farag was born on May 29, 1976 in Sohag, Egypt.
In 2000 he graduated at the Faculty of Medicine, South Valley University, Sohag, Egypt. In 2006 he completed his training as a resident of urology at the Sohag University Hospital and passed his Masters degree in Urology at Sohag University. In 2012 he passed his Doctoral degree in Urology at Sohag University and currently he is a Lecturer of urology at Sohag University, Sohag, Egypt.

Awards

1. Best EUSP Scholar 2012: granted by European Urology Scholarship Programme (EUSP) section of European Association of Urology (EAU). http://www.eauparis2012.org/the-congress/awards
2. Vision Award 2012: granted by EAU Section of Urological Imaging (ESUI) for the best imaging study published in urological literature 2011. http://www.eauparis2012.org/the-congress/awards
3. Selected to represent Europe in the 'Rising Stars Program' for the first academic exchange between the European Association of Urology and the Chinese Urological Association, November 2012.

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ABBREVIATIONS USED IN THIS THESIS

AG	Abrams/Griffiths number
AUC	Area under the curve
ATP	Adenosine triphosphate
BOO	Bladder outlet obstruction
BMI	Body mass index
BWT	Bladder wall thickness
CART	Classification and regression tree
CR	Creatinine
DO	Detrusor overactivity
DUF	Doppler ultrasound uroflowmetry
DUFV	Doppler ultrasound uroflowmetry velocity
DWT	Detrusor wall thickness
EMG	Electromyogram
EMG_{abd}	Electromyogram of abdominal muscles
ED	Erectile dysfunction
Hb_{sum}	Total hemoglobin
HHb	Deoxyhemoglobin
ICS	International Continence Society
IDC	Involuntary detrusor contractions
IPSS	International Prostate Symptom Score
IVPP	Intravesical prostatic protrusion
K_c	Cohen’s Kappa statistics
K_f	Fleiss’ Kappa statistics
LR	Likelihood ratio
LUTS	Lower urinary tract symptoms
LSQSE	Least Squares Strain Estimators
Ml/S	Milliliter per second
MUI	Mixed urinary incontinence
NIRS	Near-infrared spectroscopy
NGF	Nerve growth factor
NPV	Negative predictive value
OAB	Overactive bladder
O_2Hb	Oxyhemoglobin
P_{abd}	Abdominal pressure
P_{det}	Detrusor pressure
$P_{det.max}$	Maximum amplitude of rise in detrusor pressure
PFS	Pressure flow study
PPV	Positive predictive value
P	Level of significance
P_{ves}	Intravesical pressure
PVR	Postvoid residual
pg	Picogram
Q_{max}	Maximum urinary flow rate
Q_{ura}	Flow rate curve
QUADAS	Quality assessment of diagnostic accuracy studies
Q_{clinic}	Clinical urowflometer
$Q_{digital}$	Digital uroflowmeter

Q_{Single}	Home-based uroflowmeter
RI	Resistive index
RF	Radiofrequency
ROC	Receiver operating characteristics curve
ROI	Region-of-interest
SUI	Stress urinary incontinence
TVUS	Trans vaginal ultrasound
TAUS	Trans abdominal ultrasound
TLUS	Trans labial ultrasound
TRUS	Trans rectal ultrasound
TURP	Trans urethral resection of the prostate
UEBW	Ultrasonographic estimated bladder weight
UTI	Urinary tract infection
V	Velocity
Vin	Volume of fluid infused in the bladder
VR	Velocity ratio
Vs	Versus
$\Delta p_{det}@\varepsilon_{max}$	Detrusor pressure at maximum strain
ε_{max}	Maximum strain
µmol/l	Micromol per liter